Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	4	(("6338851") or ("6852324") or ("5847004") or ("5726166")).PN.	US-PGPUB; USPAT; EPO	OR	OFF	2005/03/30 14:39
L2	37	(nitric adj1 oxide) same (plasmodium or malaria) same (treatment or administe?)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/03/30 14:53
L3	161	(nitric adj1 oxide) same (plasmodium or malaria)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/03/30 14:54
L4	43	(nitric adj1 oxide) near20 (plasmodium or malaria)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/03/30 14:54
L5	18	(nitric adj1 oxide) same (treat? or administer?)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/03/30 14:56
L6	0	l3 and l5	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/03/30 14:55
L7	0	l5 and (plasmodium or malaria)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/03/30 14:56
L8	4961	(nitric adj1 oxide) same (treat or treated or treatment or administer or administeration)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/03/30 14:57
L9	47	l8 same (malaria or plasmodium)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/03/30 14:58

```
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TERMINAL (ENTER 1, 2, 3, OR ?):2


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 NEWS  1           Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2           "Ask CAS" for self-help around the clock
 NEWS  3  FEB 25   CA/CAPLUS - Russian Agency for Patents and Trademarks
                   (ROSPATENT) added to list of core patent offices covered
 NEWS  4  FEB 28   PATDPAFULL - New display fields provide for legal status
                   data from INPADOC
 NEWS  5  FEB 28   BABS - Current-awareness alerts (SDIs) available
 NEWS  6  FEB 28   MEDLINE/LMEDLINE reloaded
 NEWS  7  MAR 02   GBFULL: New full-text patent database on STN
 NEWS  8  MAR 03   REGISTRY/ZREGISTRY - Sequence annotations enhanced
 NEWS  9  MAR 03   MEDLINE file segment of TOXCENTER reloaded
 NEWS  10 MAR 22   KOREAPAT now updated monthly; patent information enhanced
 NEWS  11 MAR 22   Original IDE display format returns to REGISTRY/ZREGISTRY
 NEWS  12 MAR 22   PATDPASPC - New patent database available
 NEWS  13 MAR 22   REGISTRY/ZREGISTRY enhanced with experimental property tags

 NEWS EXPRESS  JANUARY 10 CURRENT WINDOWS VERSION IS V7.01a, CURRENT
               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 10 JANUARY 2005

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FILE 'HOME' ENTERED AT 16:34:44 ON 30 MAR 2005

=> file .meeting
'EVENTLINE' IS NOT A VALID FILE NAME
Enter "HELP FILE NAMES" at an arrow prompt (=>) for a list of files
that are available.  If you have requested multiple files, you can
specify a corrected file name or you can enter "IGNORE" to continue
accessing the remaining file names entered.
ENTER A FILE NAME OR (IGNORE):ignore
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       0.21       0.21

FILE 'AGRICOLA' ENTERED AT 16:34:58 ON 30 MAR 2005
```

```
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=> (nitric oxide) and malaria and (administer or treat or treatment or administration)
L1            1 FILE AGRICOLA
L2           22 FILE BIOTECHNO
L3            0 FILE CONFSCI
L4            0 FILE HEALSAFE
L5            0 FILE IMSDRUGCONF
L6           24 FILE LIFESCI
L7            0 FILE MEDICONF
L8           26 FILE PASCAL

TOTAL FOR ALL FILES
L9           73 (NITRIC OXIDE) AND MALARIA AND (ADMINISTER OR TREAT OR TREATMENT
                OR ADMINISTRATION)

=> dup rem
ENTER L# LIST OR (END):19
DUPLICATE IS NOT AVAILABLE IN 'IMSDRUGCONF, MEDICONF'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
PROCESSING COMPLETED FOR L9
L10           47 DUP REM L9 (26 DUPLICATES REMOVED)

=> l10 and py<2003
L11           1 S L10
L12           1 FILE AGRICOLA
L13          21 S L10
L14          19 FILE BIOTECHNO
L15           0 S L10
'2003' NOT A VALID FIELD CODE
L16           0 FILE CONFSCI
L17           0 S L10
L18           0 FILE HEALSAFE
L19           0 S L10
L20           0 FILE IMSDRUGCONF
L21          12 S L10
L22          11 FILE LIFESCI
L23           0 S L10
'2003' NOT A VALID FIELD CODE
L24           0 FILE MEDICONF
L25          13 S L10

<------User Break------>
```

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SEARCH ENDED BY USER

=> file .meeting
'EVENTLINE' IS NOT A VALID FILE NAME
Enter "HELP FILE NAMES" at an arrow prompt (=>) for a list of files
that are available.  If you have requested multiple files, you can
specify a corrected file name or you can enter "IGNORE" to continue
accessing the remaining file names entered.
ENTER A FILE NAME OR (IGNORE):ignore
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                      12.84      13.05

FILE 'AGRICOLA' ENTERED AT 16:41:28 ON 30 MAR 2005

FILE 'BIOTECHNO' ENTERED AT 16:41:28 ON 30 MAR 2005
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=> (nitric oxide) and malaria and (administer or treat or treatment or administration)
L26           1 FILE AGRICOLA
L27          22 FILE BIOTECHNO
L28           0 FILE CONFSCI
L29           0 FILE HEALSAFE
L30           0 FILE IMSDRUGCONF
L31          24 FILE LIFESCI
L32           0 FILE MEDICONF
L33          26 FILE PASCAL

TOTAL FOR ALL FILES
L34          73 (NITRIC OXIDE) AND MALARIA AND (ADMINISTER OR TREAT OR TREATMENT
                OR ADMINISTRATION)

=> (nitric oxide)(7A)(administer or treat or treatment or administration)
L35          19 FILE AGRICOLA
L36         320 FILE BIOTECHNO
L37          22 FILE CONFSCI
L38           1 FILE HEALSAFE
L39           0 FILE IMSDRUGCONF
L40         355 FILE LIFESCI
L41           1 FILE MEDICONF
L42        1305 FILE PASCAL

TOTAL FOR ALL FILES
L43        2023 (NITRIC OXIDE)(7A)(ADMINISTER OR TREAT OR TREATMENT OR ADMINISTR
                ATION)
```

```
=> 134 and 143
L44             0 FILE AGRICOLA
L45             1 FILE BIOTECHNO
L46             0 FILE CONFSCI
L47             0 FILE HEALSAFE
L48             0 FILE IMSDRUGCONF
L49             1 FILE LIFESCI
L50             0 FILE MEDICONF
L51             1 FILE PASCAL

TOTAL FOR ALL FILES
L52             3 L34 AND L43

=> dup rem
ENTER L# LIST OR (END):152
DUPLICATE IS NOT AVAILABLE IN 'IMSDRUGCONF, MEDICONF'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
PROCESSING COMPLETED FOR L52
L53              1 DUP REM L52 (2 DUPLICATES REMOVED)

=> d 153 ibib abs total

L53   ANSWER 1 OF 1  BIOTECHNO  COPYRIGHT 2005 Elsevier Science B.V. on STN
      DUPLICATE
ACCESSION NUMBER:         1998:28243594   BIOTECHNO
TITLE:                    Interleukin-12-dependent mechanisms in the clearance
                          of blood-stage murine malaria parasite
                          Plasmodium berghei XAT, an attenuated variant of P.
                          berghei NK65
AUTHOR:                   Yoshimoto T.; Yoneto T.; Waki S.; Nariuchi H.
CORPORATE SOURCE:         Dr. T. Yoshimoto, Dept. of Allergology, Institute of
                          Medical Science, University of Tokyo, 4-6-1
                          Shirokanedai, Minatoku, Tokyo 108-8639, Japan.
                          E-mail: yoshimot@ims.u-tokyo.ac.jp
SOURCE:                   Journal of Infectious Diseases, (1998), 177/6
                          (1674-1681), 43 reference(s)
                          CODEN: JIDIAQ  ISSN: 0022-1899
DOCUMENT TYPE:            Journal; Article
COUNTRY:                  United States
LANGUAGE:                 English
SUMMARY LANGUAGE:         English
AN    1998:28243594   BIOTECHNO
AB    The mechanism of development of host resistance to blood-stage malarial
      infection was studied by use of an irradiation-induced attenuated
      variant, Plasmodium berghei XAT, obtained from a lethal strain, P.
      berghei NK65. The infection enhanced mRNA expression of interleukin
      (IL)-12 p40 and also of interferon (IFN)-γ, IL-4, IL-10, and
      cytokine-inducible nitric oxide synthase (iNOS) in
      spleen. Treatment of these mice with anti-IL-12 or anti-
      IFN-γ led to the progression of parasitemia and fatal outcome.
      Anti-IL-12 treatment significantly reduced the secretion and
      mRNA expression of IFN-γ and greatly diminished the augmentation of
      iNOS mRNA expression. In addition, recombinant IL-12
      administration delayed the onset of parasitemia because of the
      enhanced IFN-γ production. These results suggest that blood-stage
      P. berghei XAT infection induces IL-12 production, which is important for
      the development of host resistance via IFN-γ production.


=> 143 and malaria
L54             0 FILE AGRICOLA
L55             1 FILE BIOTECHNO
L56             0 FILE CONFSCI
L57             0 FILE HEALSAFE
L58             0 FILE IMSDRUGCONF
L59             1 FILE LIFESCI
L60             0 FILE MEDICONF
```

```
L61           1 FILE PASCAL

TOTAL FOR ALL FILES
L62           3 L43 AND MALARIA

=> dup rem
ENTER L# LIST OR (END):l62
DUPLICATE IS NOT AVAILABLE IN 'IMSDRUGCONF, MEDICONF'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
PROCESSING COMPLETED FOR L62
L63            1 DUP REM L62 (2 DUPLICATES REMOVED)

=> d l63 ibib abs total

L63   ANSWER 1 OF 1  BIOTECHNO  COPYRIGHT 2005 Elsevier Science B.V. on STN
      DUPLICATE
ACCESSION NUMBER:         1998:28243594   BIOTECHNO
TITLE:                    Interleukin-12-dependent mechanisms in the clearance
                          of blood-stage murine malaria parasite
                          Plasmodium berghei XAT, an attenuated variant of P.
                          berghei NK65
AUTHOR:                   Yoshimoto T.; Yoneto T.; Waki S.; Nariuchi H.
CORPORATE SOURCE:         Dr. T. Yoshimoto, Dept. of Allergology, Institute of
                          Medical Science, University of Tokyo, 4-6-1
                          Shirokanedai, Minatoku, Tokyo 108-8639, Japan.
                          E-mail: yoshimot@ims.u-tokyo.ac.jp
SOURCE:                   Journal of Infectious Diseases, (1998), 177/6
                          (1674-1681), 43 reference(s)
                          CODEN: JIDIAQ  ISSN: 0022-1899
DOCUMENT TYPE:            Journal; Article
COUNTRY:                  United States
LANGUAGE:                 English
SUMMARY LANGUAGE:         English
AN    1998:28243594   BIOTECHNO
AB    The mechanism of development of host resistance to blood-stage malarial
      infection was studied by use of an irradiation-induced attenuated
      variant, Plasmodium berghei XAT, obtained from a lethal strain, P.
      berghei NK65. The infection enhanced mRNA expression of interleukin
      (IL)-12 p40 and also of interferon (IFN)-γ, IL-4, IL-10, and
      cytokine-inducible nitric oxide synthase (iNOS) in
      spleen. Treatment of these mice with anti-IL-12 or anti-
      IFN-γ led to the progression of parasitemia and fatal outcome.
      Anti-IL-12 treatment significantly reduced the secretion and mRNA
      expression of IFN-γ and greatly diminished the augmentation of iNOS
      mRNA expression. In addition, recombinant IL-12 administration delayed
      the onset of parasitemia because of the enhanced IFN-γ production.
      These results suggest that blood-stage P. berghei XAT infection induces
      IL-12 production, which is important for the development of host
      resistance via IFN-γ production.


=> (nitric oxide) and malaria and (administer or treat or treatment or administration or
treating or administering)
L64           1 FILE AGRICOLA
L65          23 FILE BIOTECHNO
L66           0 FILE CONFSCI
L67           0 FILE HEALSAFE
L68           0 FILE IMSDRUGCONF
L69          24 FILE LIFESCI
L70           0 FILE MEDICONF
L71          26 FILE PASCAL

TOTAL FOR ALL FILES
L72          74 (NITRIC OXIDE) AND MALARIA AND (ADMINISTER OR TREAT OR TREATMENT
                OR ADMINISTRATION OR TREATING OR ADMINISTERING)

=> dup rem
ENTER L# LIST OR (END):l64, l65, l69
```

PROCESSING COMPLETED FOR L64
PROCESSING COMPLETED FOR L65
PROCESSING COMPLETED FOR L69
L73 35 DUP REM L64, L65, L69 (13 DUPLICATES REMOVED)

=> l73 and py<1999
L74 1 S L73
L75 0 FILE AGRICOLA
L76 22 S L73
L77 11 FILE BIOTECHNO
L78 0 S L73
'1999' NOT A VALID FIELD CODE
L79 0 FILE CONFSCI
L80 0 S L73
L81 0 FILE HEALSAFE
L82 0 S L73
L83 0 FILE IMSDRUGCONF
L84 12 S L73
L85 6 FILE LIFESCI
L86 0 S L73
'1999' NOT A VALID FIELD CODE
L87 0 FILE MEDICONF
L88 0 S L73
L89 0 FILE PASCAL

TOTAL FOR ALL FILES
L90 17 L73 AND PY<1999

=> d l90 ibib abs total

L90 ANSWER 1 OF 17 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 1998:28267842 BIOTECHNO
TITLE: A pathogenic role of IL-12 in blood-stage murine **malaria** lethal strain Plasmodium berghei NK65 infection
AUTHOR: Yoshimoto T.; Takahama Y.; Wang C.-R.; Yoneto T.; Waki S.; Nariuchi H.
CORPORATE SOURCE: Dr. T. Yoshimoto, Department of Allergology, Institute of Medical Science, University of Tokyo, 4-6-1 Shirokanedai, Minato-ku, Tokyo 108-8639, Japan.
SOURCE: Journal of Immunology, **(01 JUN 1998)**, 160/11 (5500-5505), 55 reference(s)
CODEN: JOIMA3 ISSN: 0022-1767
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1998:28267842 BIOTECHNO
AB We studied whether the infection with a blood-stage murine **malaria** lethal Plasmodium berghei NK65 induces IL-12 production, and if so, how the IL-12 production is involved in the protection or pathogenesis. The infection of C57BL/6 mice enhanced mRNA expression of IL-12 p40 and also IFN-γ, IL-4, and IL-10 in both spleen and liver during the early course of the infection. It also enhanced the mRNA expression of TNF-α, Fas ligand, and cytokine- inducible **nitric oxide** synthase. Increased IL-12 p40 production was also observed in the culture supernatant of spleen cells and in sera of infected mice. In addition, the infection caused massive liver injury with elevated serum glutamic-oxaloacetic transaminase and serum glutamic-pyruvic transaminase activities and body weight loss. **Treatment** of these infected mice with neutralizing mAb against IL-12 prolonged the survival and diminished the liver injury with reduced elevation of serum serum glutamic- oxaloacetic transaminase and serum glutamic-pyruvic transaminase activities and decreased body weight loss. However, the anti-IL-12 **treatment** did not affect parasitemia, and all these mice eventually died. Similar results were obtained when infected mice were treated with neutralizing mAb against IFN- γ. Moreover, anti-IL-12 **treatment** greatly reduced the secretion

and mRNA expression of IFN-γ in both spleen and liver. These results suggest that the lethal P. berghei NK65 infection induces IL-12 production and that the IL-12 is involved in the pathogenesis of liver injury via IFN-γ production rather than the protection.

L90 ANSWER 2 OF 17 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 1998:28243594 BIOTECHNO
TITLE: Interleukin-12-dependent mechanisms in the clearance of blood-stage murine **malaria** parasite Plasmodium berghei XAT, an attenuated variant of P. berghei NK65
AUTHOR: Yoshimoto T.; Yoneto T.; Waki S.; Nariuchi H.
CORPORATE SOURCE: Dr. T. Yoshimoto, Dept. of Allergology, Institute of Medical Science, University of Tokyo, 4-6-1 Shirokanedai, Minatoku, Tokyo 108-8639, Japan. E-mail: yoshimot@ims.u-tokyo.ac.jp
SOURCE: Journal of Infectious Diseases, (**1998**), 177/6 (1674-1681), 43 reference(s) CODEN: JIDIAQ ISSN: 0022-1899
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1998:28243594 BIOTECHNO
AB The mechanism of development of host resistance to blood-stage malarial infection was studied by use of an irradiation-induced attenuated variant, Plasmodium berghei XAT, obtained from a lethal strain, P. berghei NK65. The infection enhanced mRNA expression of interleukin (IL)-12 p40 and also of interferon (IFN)-γ, IL-4, IL-10, and cytokine-inducible **nitric oxide** synthase (iNOS) in spleen. **Treatment** of these mice with anti-IL-12 or anti-IFN-γ led to the progression of parasitemia and fatal outcome. Anti-IL-12 **treatment** significantly reduced the secretion and mRNA expression of IFN-γ and greatly diminished the augmentation of iNOS mRNA expression. In addition, recombinant IL-12 **administration** delayed the onset of parasitemia because of the enhanced IFN-γ production. These results suggest that blood-stage P. berghei XAT infection induces IL-12 production, which is important for the development of host resistance via IFN-γ production.

L90 ANSWER 3 OF 17 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 1997:27138285 BIOTECHNO
TITLE: Prolonged Th1-like response generated by a Plasmodium yoelii-specific T cell clone allows complete clearance of infection in reconstituted mice
AUTHOR: Amante F.H.; Good M.F.
CORPORATE SOURCE: M.F. Good, Coop. Res. Ctr. for Vaccine Technol., Queensland Inst. of Medical Research, PO Royal Brisbane Hospital, Brisbane, QLD 4029, Australia.
SOURCE: Parasite Immunology, (**1997**), 19/3 (111-126), 37 reference(s) CODEN: PAIMD8 ISSN: 0141-9838
DOCUMENT TYPE: Journal; Article
COUNTRY: United Kingdom
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1997:27138285 BIOTECHNO
AB In the present study, we report the ability of in vitro cultured CD4.sup.+ T cells, generated following immunization with dead blood stage P. yoelii parasites, to mediate protection against homologous challenge infection in reconstituted nude mice. P. yoelii-specific T cell line cells produced IFN-γ after in vitro stimulation with specific antigen, and were protective when adoptively transferred into athymic nude mice. Following transfer of P. yoelii-specific T cell lines into nude and SCID mice, elevated levels of **nitric oxide** (NO) were detected during the first week of infection at a time when parasitaemias were suppressed. However, in vivo blocking of NO production through **administration** of L-NMMA, an inhibitor of NO synthase,

increased mortality, but did not alter the course of primary parasitaemia in P. yoelii-specific T cell line-reconstituted nude mice. In addition, a P. yoelii-specific CD4.sup.+ T cell clone, which produced IFN-γ in vitro, afforded sterile protection via mechanisms other than NO. By ELISA, antibodies were undetectable on all but one day (day 79) post T cell clone transfer and parasite challenge, where very low levels of antibodies were detected, with some evidence of recognition of **malaria** proteins by Western blot. Collectively, our data suggest that T cell effector functions, independent of NO production and in the absence of high levels of parasite-specific antibodies, can contribute to sterile immunity to P. yoelii.

L90 ANSWER 4 OF 17 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 1996:26009339 BIOTECHNO
TITLE: In vivo regulation of **nitric oxide** production by tumor necrosis factor alpha and gamma interferon, but not by interleukin-4, during blood stage **malaria** in mice
AUTHOR: Jacobs P.; Radzioch D.; Stevenson M.M.
CORPORATE SOURCE: Center for Study of Host Resistance, McGill University, Montreal General Hosp. Res. Inst., 1650 Cedar Ave.,Montreal, Que. H3G 1A4, Canada.
SOURCE: Infection and Immunity, (**1996**), 64/1 (44-49)
CODEN: INFIBR ISSN: 0019-9567
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1996:26009339 BIOTECHNO
AB We investigated whether gamma interferon (IFN-γ; a Th1 cytokine), tumor necrosis factoe alpha (TNF-α), and interleukin-4 (IL-4; a Th2 cytokine) modulate **nitric oxide** (NO) production in vivo during blood stage infection with Plasmodium chabaudi AS. **Treatment** of resistant C57BL/6 mice, which resolve infection with P. chabaudi AS and produce increased levels of IFN- γ, TNF-α, and NO early during infection, with anti-IFN-γ plus anti-TNF-σ monoclonal antibodies (MAbs) resulted in a reduction of both splenic inducible NO synthase mRNA and serum NO.sub.3.sup.- levels by 50 and 100%, respectively. **Treatment** with the anti-TNF-α MAb alone reduced only serum NO.sub.3.sup.- levels by 35%, and **treatment** with the anti-IFN-γ MAb alone had no effect on NO production by these mice during infection. Susceptible A/J mice, which succumb to infection with P. chabaudi AS and produce increased levels of IL-4 but low levels of IFN-γ, TNF-α, and NO early during infection, were treated with an anti-IL-4 MAb. The latter **treatment** had no effect on NO production by this mouse strain during infection. In addition, our results also demonstrate that **treatment** of resistant C57BL/6 mice with anti-IFN-γ plus anti-TNF-α MAbs affects, in addition to NO production, other traits of resistance to P. chabaudi AS **malaria** such as the peak level of parasitemia and the development of splenomegaly. Furthermore, the change in spleen weight was shown to be an IFN-γ-independent effect of TNF-α. **Treatment** of susceptible A/J mice during infection with an anti-IL-4 MAb had no effect on these markers of resistance. Thus, these results demonstrate that TNF-α and IFN-γ are critical in the regulation of NO production and other traits of resistance during P. chabaudi AS **malaria** in C57BL/6 mice. These data also indicate that **treatment** with an anti-IL-4 antibody alone is not able to induce NO production or confer resistance to A/J mice against P. chabaudi AS **malaria**.

L90 ANSWER 5 OF 17 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 1995:25353607 BIOTECHNO
TITLE: **Nitric oxide** expression in the spleen, but not in the liver, correlates with resistance to blood-stage **malaria** in mice
AUTHOR: Jacobs P.; Radzioch D.; Stevenson M.M.
CORPORATE SOURCE: Center for Study of Host Resistance, Montreal Gen.

Hosp. Research Inst., 1650 Cedar Avenue,Montreal, Que. H3G 1A4, Canada.
SOURCE: Journal of Immunology, (**1995**), 155/11 (5306-5313)
CODEN: JOIMA3 ISSN: 0022-1767
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1995:25353607 BIOTECHNO
AB The production and function of **nitric oxide** during the early phase of blood-stage infection with Plasmodium chabaudi AS was analyzed using two inbred strains of mice that differ in the level of resistance to this parasite. Northern blot analysis of in vivo expression of inducible **nitric oxide** synthase (iNOS) revealed that early during infection resistant C57BL/6 mice, which clear the infection by 4 wk, have higher levels of iNOS mRNA in the spleen than susceptible A/J mice. In contrast, susceptible A/J mice have significantly increased levels of iNOS mRNA in the liver later in the course of infection just before death occurs. Splenic macrophages recovered from resistant C57BL/6 mice on day 7 postinfection express iNOS mRNA which is up- regulated following overnight stimulation of the cells with LPS. Furthermore, during the first week postinfection, splenic macrophages recovered from resistant hosts produce significantly higher levels of nitrite (NO.sub.2.sup.-) in vitro in response to LPS than similarly stimulated macrophages from susceptible A/J mice. Increased levels of nitrate (NO.sub.3.sup.-) were only detected in serum of resistant C57BL/6 mice at the time of peak parasitemia. **Treatment** with the iNOS inhibitor, aminoguanidine, reduced NO.sub.3.sup.- levels in serum of C57BL/6 mice and eliminated resistance of these hosts to P. chabaudi AS **malaria** without affecting parasitemia. These results demonstrate that the ability to produce high amounts of **nitric oxide** (NO) early during infection with blood-stage P. chabaudi AS correlates with resistance, but that NO may not be involved in parasite killing. Moreover, the tissue site of NO production, that is, spleen vs liver, appears to be critical and correlates with resistance vs susceptibility to P. chabaudi AS **malaria**, respectively.

L90 ANSWER 6 OF 17 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 1995:25263620 BIOTECHNO
TITLE: IL-12-induced protection against blood-stage Plasmodium chabaudi AS requires IFN-γ and TNF-α and occurs via a **nitric oxide**-dependent mechanism
AUTHOR: Stevenson M.M.; Mi Fong Tam; Wolf S.F.; Sher A.
CORPORATE SOURCE: Montreal Gen. Hosp. Research Inst., 1650 Cedar Avenue,Montreal, Que. H3G 1A4, Canada.
SOURCE: Journal of Immunology, (**1995**), 155/5 (2545-2556)
CODEN: JOIMA3 ISSN: 0022-1767
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1995:25263620 BIOTECHNO
AB The effects of IL-12 **administration** on the development of protective immunity to blood-stage Plasmodium chabaudi AS were analyzed. **Treatment** of susceptible A/J mice on the day of infection and for 5 days postinfection with various doses (0.025-0.3 μg) of rIL-12 significantly decreased the peak parasitemia level, but only **treatment** with 0.1 μg resulted in increased survival. **Treatment** of resistant 86 mice with 0.1 μg of rIL-12 using the same regimen also significantly decreased the peak parasitemia level, but 40% of the animals died. **Treatment** of these mice with anti-IL-12 mAb resulted in a more severe course of infection, but survival was not significantly altered. The mechanism of IL-12-induced resistance was examined in A/J mice during infection. Compared with

spleen cells from untreated mice, cells from IL-12-treated mice produced significantly higher levels of IFN-γ spontaneously as well as in response to Con A or Ag stimulation on day 7 postinfection. Significantly higher levels of IFN-γ and TNF-α were found in the sera of IL-12-treated mice, which correlated with high levels of the **nitric oxide** (NO) metabolite, NO.sub.3.sup.-. Furthermore, CD4.sup.+ T cell depletion was found to abrogate IL-12-induced resistance. **Administration** of neutralizing mAb against IFN-γ or TNF-α to IL-12-treated mice showed that simultaneous depletion of both cytokines resulted in 100% mortality. The role of NO was investigated by **administration** of aminoguanidine, a selective inhibitor of cytokine-inducible **nitric oxide** synthase, to IL-12-treated mice. Significantly increased mortality was observed following **treatment** twice daily with 9 mg of aminoguanidine, but there was no effect on parasitemia. In conclusion, these results demonstrate that IL-12 regulates the development of resistance to P. chabaudi AS via a CD4.sup.+ Th1 response, which involves the cytokines IFN-γ and TNF-α, and is in part NO dependent. Therefore, IL-12, given in the appropriate dose, may be useful in the induction of protective immunity to blood-stage **malaria**.

L90 ANSWER 7 OF 17 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 1994:24329066 BIOTECHNO
TITLE: Interleukin 12 induction of interferon γ-dependent protection against **malaria**
AUTHOR: Sedegah M.; Finkelman F.; Hoffman S.L.
CORPORATE SOURCE: Malaria Program, Naval Medical Research Institute,Bethesda, MD 20889-5607, United States.
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (**1994**), 91/22 (10700-10702)
CODEN: PNASA6 ISSN: 0027-8424
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1994:24329066 BIOTECHNO
AB Intraperitoneal injection of recombinant Interleukin 12 (rIL-12) at 30 ng/day for 5 days beginning 1 to 2 days before sporozoite challenge or **administration** of a single dose of 150 ng of rIL-12 2 days before challenge protected 100% of BALB/c mice against challenge with 10.sup.2 Plasmodium yoelii sporozoites. rIL-12-induced protection was eliminated in all mice by **administration** of a monoclonal antibody against interferon γ and in 50% of mice by **administration** of N(G)-monomethyl-L-arginine, a competitive inhibitor of **nitric oxide** synthase. rIL-12 protected BALB/c mice treated with cytotoxic anti-CD4 and anti-CD8 monoclonal antibodies, as well as T-cell- and B-cell- deficient severe combined immunodeficiency mice. These data suggest that rIL- 12 stimulates non-B, non-T cells to produce interferon γ that kills intrahepatic parasites by stimulating **nitric oxide** production. If rIL-12 proves to be well tolerated by humans, our findings support consideration of rIL-12 as an immunoprophylactic against **malaria**.

L90 ANSWER 8 OF 17 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 1994:24228080 BIOTECHNO
TITLE: Tumor necrosis factor and interleukin-1 synergy in the context of **malaria** pathology
AUTHOR: Rockett K.A.; Awburn M.M.; Rockett E.J.; Clark I.A.
CORPORATE SOURCE: John Curtin School of Med. Research, Australian National University,Canberra, ACT 2601, Australia.
SOURCE: American Journal of Tropical Medicine and Hygiene, (**1994**), 50/6 (735-742)
CODEN: AJTHAB ISSN: 0002-9637
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English

SUMMARY LANGUAGE: English
AN 1994:24228080 BIOTECHNO
AB Reports linking human malarial illness and pathology with serum tumor necrosis factor (TNF) levels are now common, although the association is not always precise. Possible reasons for this discrepancy include the reported variation in levels of interleukin-1 (IL-1), a cytokine known to synergize with TNF. We have examined the extent of synergy between recombinant human TNF and either recombinant human IL-1α or recombinant human IL-1β in producing hypoglycemia and increasing plasma levels of **nitric oxide** in **malaria** (Plasmodium vinckei)-infected CBA mice. Very low concentrations of either IL-1α or IL-1β, with negligible effects on their own, greatly enhanced the effectiveness of TNF in bringing about these changes. In particular, synergy in generating **nitric oxide**, a mediator argued to induce cerebral **malaria**, was profound. Thus, variation in generation of IL-1 during infection provides one explanation for the poor correlation sometimes encountered between serum TNF levels and clinical condition.

L90 ANSWER 9 OF 17 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 1993:23101073 BIOTECHNO
TITLE: In vivo induction of the **nitric oxide** pathway in hepatocytes after injection with irradiated **malaria** sporozoites, **malaria** blood parasites or adjuvants
AUTHOR: Nussler A.K.; Renia L.; Pasquetto V.; Miltgen F.; Matile H.; Mazier D.
CORPORATE SOURCE: Department of Surgery, University of Pittsburgh,Pittsburgh, PA 15261, United States.
SOURCE: European Journal of Immunology, (**1993**), 23/4 (882-887)
CODEN: EJIMAF ISSN: 0014-2980
DOCUMENT TYPE: Journal; Article
COUNTRY: Germany, Federal Republic of
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1993:23101073 BIOTECHNO
AB The mechanisms responsible for malarial immunity induced by repetitive injections of X-irradiated sporozoites have not been fully established. We demonstrate here that a single injection of irradiated sporozoites induced, as soon as 24 h after, a non-permissive state to hepatocyte reinfection with sporozoites in vitro. The same effect was observed when malarial blood forms, irradiated promastigotes of Leishmania infantum, adjuvants (muramyl dipeptide, poly acidylic uridylic) or interferon-γ was injected. Activation of the **nitric oxide** (NO) pathway in the hepatocyte by these factors was found to be responsible for hepatocyte refractory status. Additionally, this metabolic pathway is involved in protection given by repeated injections of irradiated sporozoites since protection could be reversed by **treating** mice at the time of sporozoite challenge with a competitive inhibitor (N(G)-monomethyl-L-arginine) of the NO pathway. These results suggest that, in view of an antisporozoite vaccine, further studies are needed to find out how to activate specifically a long-lasting nonspecific immune response.

L90 ANSWER 10 OF 17 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 1992:22333821 BIOTECHNO
TITLE: Interferon-γ induced lethality in the late phase of Plasmodium vinckei **malaria** despite effective parasite clearance by chloroquine
AUTHOR: Kremsner P.G.; Neifer S.; Chaves M.F.; Rudolph R.; Bienzle U.
CORPORATE SOURCE: Landesinstitut Tropenmedizin Berlin, Engeldamm 62,1020 Berlin, Germany.
SOURCE: European Journal of Immunology, (**1992**), 22/11 (2873-2878)
CODEN: EJIMAF ISSN: 0014-2980
DOCUMENT TYPE: Journal; Article

COUNTRY: Germany, Federal Republic of
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1992:22333821 BIOTECHNO
AB A combination therapy was tested consisting of chloroquine and interferon-γ (IFN-γ) in the late phase of blood-stage Plasmodium vinckei **malaria** in BALB/c mice. When mice were treated with three times 300 μg chloroquine at 24-h intervals starting at a parasitemia of 30%-50%, only 5 of 14 mice (36%) died 2-4 days after initiation of therapy. However, when infected mice received chloroquine plus 1 μg IFN-γ at the same time, 14 of 18 mice (78%) died 0.5-3 days after start of therapy ($p < 0.05$) despite clearance of parasitemia. The histopathology from mice dying after combination therapy revealed interstitial leukocyte infiltration of lung tissue, severe liver cell necrosis and kidney tubular necrosis. Pretreatment of P.vinckei-infected mice with pentoxifylline, a phosphodiesterase inhibitor, led to a significant decrease of IFN-γ-induced lethality ($p < 0.05$). In contrast, pretreatment with neutralizing antibodies to tumor necrosis factor or with L-N-monomethyl arginine, the latter an inhibitor of the **nitric oxide** synthase, significantly increased lethality ($p < 0.05$).

L90 ANSWER 11 OF 17 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 1990:20260837 BIOTECHNO
TITLE: Cellular mechanisms of nonspecific immunity to intracellular infection: Cytokine-induced synthesis of toxic nitrogen oxides from L-arginine by macrophages and hepatocytes
AUTHOR: Green S.J.; Mellouk S.; Hoffman S.L.; Meltzer M.S.; Nacy C.A.
CORPORATE SOURCE: Department of Cellular Immunology, Walter Reed Army Institute of Research, Washington, DC, United States.
SOURCE: Immunology Letters, (**1990**), 25/1-3 (15-19)
CODEN: IMLED6 ISSN: 0165-2478
DOCUMENT TYPE: Journal; Conference Article
COUNTRY: Netherlands
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1990:20260837 BIOTECHNO
AB **Nitric oxide** (NO) produced by cytokine-treated macrophages and hepatocytes plays a vital role in protective host responses to infectious pathogens. NO inhibits iron-sulfur-dependent enzymes involved in cellular respiration, energy production, and reproduction. Synthesis of L-arginine-derived nitrite (NO.sub.2.sup.-), the oxidative end product of NO, directly correlates with intracellular killing of Leishmania major, an obligate intracellular protozoan parasite of macrophages: the level of NO.sub.2.sup.- production is a quantitative index for macrophage activation. The competitive inhibitor of NO synthesis, monomethylarginine (N(G)MMLA), inhibits both parasite killing and NO.sub.2.sup.- production. For Leishmania, the parasite itself participates in the regulation of this toxic effector mechanism. This participation is mediated by parasite induction of tumor necrosis factor α (TNFα), an autocrine factor of macrophages: NO synthesis by interferon-γ (IFN-γ)-treated cells can be blocked by monoclonal antibodies to TNFα. NO production by IFN-γ-treated hepatocytes is of special interest in **malaria** infections: sporozoite-infected hepatocytes kill the intracellular **malaria** parasite after **treatment** with IFNγ; this killing is inhibited by N(G)MMLA.

L90 ANSWER 12 OF 17 LIFESCI COPYRIGHT 2005 CSA on STN
ACCESSION NUMBER: 2000:100606 LIFESCI
TITLE: Infected host serum blocks transmission of Plasmodium yoelii via a **nitric oxide**-dependent mechanism
AUTHOR: Cao, Ya-Ming; Tsuboi, Takafumi; Liu, Ying-Jie; Torii, Motomi*
CORPORATE SOURCE: Department of Parasitology, Ehime University School of

Medicine, Shigenobu-cho, Ehime 791-0295, Japan; E-mail: torii@m.ehime-u.ac.jp
SOURCE: Parasitology International [Parasitol. Int.], (**19980900**) vol. 47, no. 3, pp. 225-232. ISSN: 1383-5769.
DOCUMENT TYPE: Journal
FILE SEGMENT: K
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The present study was carried out to clarify whether NO mediates the 'crisis serum' induced transmission-blocking of Plasmodium yoelii to the mosquito vector. Mouse serum, obtained 5 days after P. yoelii infection (D5 serum), was administered intravenously into the mice 3 days after P. yoelii infection, followed 4-8 h later by a mosquito feed. The D5 serum demonstrated a marked suppression of oocyst development. Four hours after D5 serum injection to the mice on day 3 after P. yoelii infection, spleens were removed from the mice, and increased levels of nitrite were observed in the spleen cell culture supernatants. The contribution of NO to the D5 serum induced suppression of oocyst formation was investigated using L-NMMA, a selective inhibitor of **nitric oxide** synthase. The reduction of oocyst formation in the mosquito midgut caused by the injection of D5 serum was reversed by the **administration** of L-NMMA to the mice. Moreover, **malaria** parasitized red blood cell extract possessing the ability to induce NO in mouse spleens also showed the same inhibitory effects on oocyst formation as D5 serum. Together, these results suggest that the D5 serum may contain a parasitized red blood cell derived substance(s) which induce the NO production from host effector cells, and then inhibits the transmission of **malaria** parasites to the mosquito vector.

L90 ANSWER 13 OF 17 LIFESCI COPYRIGHT 2005 CSA on STN
ACCESSION NUMBER: 2000:100200 LIFESCI
TITLE: **Nitric oxide** inhibits the development of Plasmodium yoelii gametocytes into gametes
AUTHOR: Cao, Ya-Ming; Tsuboi, T.; Torii, M.*
CORPORATE SOURCE: Department of Parasitology, Ehime University School of Medicine, Shigenobu-cho, Ehime 791-0295, Japan; E-mail: torii@m.ehime-u.ac.jp
SOURCE: Parasitology International [Parasitol. Int.], (**19980600**) vol. 47, no. 2, pp. 157-166. ISSN: 1383-5769.
DOCUMENT TYPE: Journal
FILE SEGMENT: K
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The infectivity of gametocytes to the mosquito vector decreases dramatically during the early phase of plasmodial infection despite an increase in the number of gametocytes. The present study was aimed to clarify the mechanism of this natural transmission-blocking by using the murine **malaria** parasite, Plasmodium yoelii. The development of cultured gametocytes taken from the mice on days 4 and 5 after infection was significantly impaired; however, gametocytes taken from the mice on day 3 developed normally into ookinetes. These results indicated that the gametocyte infectivity was already lost in the infected host. The contribution of **nitric oxide** to diminished gametocyte infectivity was confirmed using L-NMMA, a selective inhibitor of **nitric oxide** synthase, and NOC5, a **nitric oxide** donor. The reduction of oocyst formation was partially reversed on day 4 after P. yoelii infection in the L-NMMA-treated group. The prevalence of infection among mosquitoes fed on mice 5 days after P. yoelii infection increased dramatically by the L-NMMA **treatment**. Moreover, the number of oocysts per mosquito midgut fed on the NOC5-treated mice infected with P. yoelii significantly decreased; likewise, gamete/zygote formation in vitro was inhibited by the pre-incubation of gametocytes with NOC5 before the gametogenesis. These results suggest that **nitric oxide**, as an effector molecule, inhibits the development of P. yoelii gametocytes into gametes.

L90 ANSWER 14 OF 17 LIFESCI COPYRIGHT 2005 CSA on STN
ACCESSION NUMBER: 1998:82438 LIFESCI
TITLE: Upregulation of reactive oxygen and nitrogen intermediates in Plasmodium berghei infected mice after rescue therapy with chloroquine or artemether
AUTHOR: Prada, J.; Mueller, S.; Bienzle, U.; Kremsner, P.G.*
CORPORATE SOURCE: Sektion Humanparasitologie, Institut fuer Tropenmedizin, Universitaet Tuebingen Wilhelmstrasse 27, D-72074, Tuebingen, Germany
SOURCE: J. ANTIMICROB. CHEMOTHER., (**19960700**) vol. 38, no. 1, pp. 95-102.
ISSN: 0305-7453.
DOCUMENT TYPE: Journal
FILE SEGMENT: K
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Plasmodium berghei ANKA infected C57B1/6 mice develop cerebral **malaria** at a parasitaemia of 15-25%. When parasitaemia reached 10%, P. berghei infected mice were treated with artemether, chloroquine or clindamycin in order to prevent the occurrence of cerebral **malaria** . Artemether and chloroquine were highly efficient. Functional tests revealed that zymosan stimulated spleen cells from untreated mice with cerebral **malaria** showed a slight decrease in their capacity to produce reactive oxygen intermediates (ROI) when compared with naive mice. After artemether or chloroquine **treatment**, the ROI production was significantly enhanced. The interferon-gamma induced production of reactive nitrogen intermediates (RNI) was slightly elevated in mice with cerebral **malaria**, but markedly elevated in artemether or chloroquine treated mice when compared with naive mice. Moreover, high levels of inducible **nitric oxide** synthase gene expression could be detected by in-situ hybridization in spleen sections of mice which had been treated with artemether or chloroquine. These findings suggest that increased production of ROI and RNI after chemotherapy may play a protective role for the host during **malaria**.

L90 ANSWER 15 OF 17 LIFESCI COPYRIGHT 2005 CSA on STN
ACCESSION NUMBER: 97:114544 LIFESCI
TITLE: Complete protective immunity induced in mice by immunization with the 19-kilodalton carboxyl-terminal fragment of the merozoite surface protein-1 (MSP1 sub(19)) of Plasmodium yoelii expressed in Saccharomyces cerevisiae. Correlation of protection with antigen-specific antibody titer, but not with effector CD4 super(+) T cells
AUTHOR: Hirunpetcharat, C.; Tian, Jing-Hui; Kaslow, D.C.; Van Rooijen, N.; Kumar, S.; Berzofsky, J.A.; Miller, L.H.; Good, M.F.*
CORPORATE SOURCE: Queensland Inst. Med. Res., P.O. Royal Brisbane Hosp., Brisbane 4029, Australia
SOURCE: J. IMMUNOL., (**19971000**) vol. 159, no. 7, pp. 3400-3411.
ISSN: 0022-1767.
DOCUMENT TYPE: Journal
FILE SEGMENT: F; K
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The 19-kDa carboxyl-terminal fragment of the merozoite surface protein-1 (MSP1) is a leading **malaria** vaccine candidate but is unable to induce immunity in all monkeys or all strains of mice. The mechanism of immunity is unclear, although data show that cell-mediated immunity plays a critical role following immunization with the larger mature MSP1 protein. We optimized a vaccine protocol using the MSP1 sub(19) fragment of Plasmodium yoelii expressed in Saccharomyces cerevisiae, such that following exposure of mice to parasites, they remained undetectable in peripheral blood, whereas control animals all died at very high parasitemia within 10 days. We then depleted the vaccinated mice of >99% of CD4 super(+) T cells by anti-CD4 mAb **treatment** and could show that infections in most animals remained subpatent following challenge.

Furthermore, mice in which the gene for the mu -chain of Ig had been disrupted could not be immunized with MSP1 sub(19). Immunity in normal mice did not depend on the presence of an intact spleen nor production of **nitric oxide**, persisting unabated when >70% of splenic macrophages were depleted. Thus, while effector CD4 super(+) T cells may contribute to immunity, neither they nor factors associated with a Th1-type cell mediated immune response appeared to play the major role in MSP1 sub(19)-induced protection in normal mice. Furthermore, T cells were not sufficient for immunity in mice lacking B cells. In normal mice, protection correlated with a very high titer of MSP1 sub(19)-specific Abs (>6,400,000), predominantly G1 and G2b, which may function by merozoite neutralization.

L90 ANSWER 16 OF 17 LIFESCI COPYRIGHT 2005 CSA on STN
ACCESSION NUMBER: 97:45603 LIFESCI
TITLE: The heme moiety of **malaria** pigment (beta -hematin) mediates the inhibition of **nitric oxide** and tumor necrosis factor alpha production by lipopolysaccharide-stimulated macrophages
AUTHOR: Taramelli, D.; Basilico, N.; Pagani, E.; Grande, R.; Monti, D.; Ghione, M.; Olliaro, P.
CORPORATE SOURCE: Istituto di Microbiologia Medica, Univ. di Milano, Via Pascal 36, 20133 Milano, Italy
SOURCE: EXP. PARASITOL., (**1995**) vol. 81, no. 4, pp. 501-511.
ISSN: 0014-4894.
DOCUMENT TYPE: Journal
FILE SEGMENT: K
LANGUAGE: English
SUMMARY LANGUAGE: English
AB To investigate the effect of the heme moiety of **malaria** pigment, hemozoin, on phagocyte functions, mouse macrophages were fed with insoluble beta -hematin, the synthetic heme-polymer chemically identical to the native pigment, or the soluble monomer, hematin. Production of inflammatory cytokines, interleukin 1 (IL1), tumor necrosis factor alpha (TNF alpha), and **nitric oxide** (NO) was assayed in the supernatants after stimulation with lipopolysaccharide. The results indicate that both beta -hematin and hematin induce a dose-dependent inhibition of macrophage production of TNF alpha and NO, but not of IL1. One-hour pretreatment with soluble hematin inhibited production of cytotoxic mediators by more than 50% compared to controls, while 6-hr exposure was necessary for insoluble beta -hematin to induce the same level of inhibition. However, the same **treatment** did not modify the production of TNF alpha and NO by mouse microglia cell lines. The inhibition was partially counterbalanced by adding sulphydryl group donors such as 2-mercaptoethanol, glutathione, or N-acetyl-cysteine during the preincubation time. The results of the present study confirm the inhibitory role of **malaria** pigment and show that such effect is due to the heme moiety and may be selective for the production of cytotoxic mediators by specific phagocytes. The implications of these findings in the control of **malaria** infection and disease and in the pathogenesis of severe **malaria** are discussed.

L90 ANSWER 17 OF 17 LIFESCI COPYRIGHT 2005 CSA on STN
ACCESSION NUMBER: 93:61277 LIFESCI
TITLE: **Nitric oxide** and cerebral **malaria**.
AUTHOR: Senaldi, G.; Kremsner, P.G.; Grau, G.E.
CORPORATE SOURCE: WHO Immunol. Res. and Train. Cent., Dep. Pathol., Univ. Geneva, 1211 Geneva, Switzerland
SOURCE: LANCET., (**1992**) vol. 340, no. 8834-8835, p. 1554.
DOCUMENT TYPE: Journal
FILE SEGMENT: K
LANGUAGE: English
AB Dr. Clark and colleagues draw attention to features shared by cerebral **malaria**, heat stroke, postoperative transitory syndrome, and the neurological syndrome that may develop as a result of **treatment** with tumour necrosis factor (TNF) or interleukin-2 (IL-2). Some features

(mental disturbances such as coma and seizures, and high concentrations of circulating proinflammatory cytokines such as TNF and IL-1) are reversible in non-fatal cases; but, cerebral **malaria**, for example, is invariably lethal if untreated. Clark and colleagues postulate that **nitric oxide** (NO) represents the physiopathological link between mental disturbances and cytokine concentrations: cytokines would induce the synthesis of NO in the vascular wall of the brain circulation, which would then diffuse into the brain parenchyma and affect neurological function. We present experimental data that do not support this view.

strains (CQR6 and CQR30) were selected in vivo from the sensitive strain NK65. Drug effects were checked both by monitoring the evolution of parasitaemia and by the survival of infected mice. In addition, intra-parasite levels of GSH and G6PD activity were measured before and after the **treatment**. Results demonstrate that acquisition of CQ resistance in P. berghei is associated with a significant increase in parasite G6PD activity and GSH level. Combination of CQ with DHEAS or buthionin sulfoximin (BSO, a specific inhibitor of GSH synthesis) significantly increased sensitivity of resistant parasites to CQ and increased the survival period of the infected mice. This reduction of parasitaemia and improvement of the survival of infected mice were associated with intra-parasite depletion of GSH and inhibition of G6PD activity due to DHEAS action. This experimental study suggests that DHEAS could be used to potentiate antimalarial action of CQ, particularly on CQ resistant strains.

L28 ANSWER 3 OF 30 LIFESCI COPYRIGHT 2005 CSA on STN
ACCESSION NUMBER: 2004:23900 LIFESCI
TITLE: Native and Inhibited Structure of a Mu class-related **Glutathione** S-transferase from **Plasmodium** falciparum
AUTHOR: Perbandt, M.; Burmeister, C.; Walter, R.D.; Betzel, C.; Liebau, E.
CORPORATE SOURCE: Institute of Biochemistry and Molecular Biology I, Center for Experimental Medicine, University Hospital Eppendorf, DESY, Building 22 A, Notkestrasse 85, 22603 Hamburg, Germany; E-mail: markus.perbandt@desy.de
SOURCE: Journal of Biological Chemistry [J. Biol. Chem.], (20040109) vol. 279, no. 2, pp. 1336-1342.
ISSN: 0021-9258.
DOCUMENT TYPE: Journal
FILE SEGMENT: K
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The parasite Plasmodium falciparum causes malaria tropica, the most prevailing parasitic disease worldwide, with 300-500 million infections and 1.5- 2.7 million deaths/year. The emergence of strains resistant to drugs used for prophylaxis and **treatment** and no vaccine available makes the structural analysis of potential drug targets essential. For that reason, we analyzed the three-dimensional structure of the glutathione S-transferase from P. falciparum (Pf-GST1) in the apoform and in complex with its inhibitor S-hexyl-glutathione. The structures have been analyzed to 2.6 and 2.2 Aa, respectively. Pf-GST1 shares several structural features with the Mu-type GSTs and is therefore closely related to this class, even though alignments with its members display low sequence identities in the range of 20-33%. Upon S-hexyl-glutathione binding, the overall structure and the glutathione-binding site (G-site) remain almost unchanged with the exception of the flexible C terminus. The detailed comparison of the parasitic enzyme with the human host Mu-class enzyme reveals that, although the overall structure is homologue, the shape of the hydrophobic binding pocket (H-site) differs substantially. In the human enzyme, it is shielded from one side by the large Mu-loop, whereas in Pf-GST1 the Mu-loop is truncated and the space to recognize and bind voluminous substrates is extended. This structural feature can be exploited to support the design of specific and parasite-selective inhibitors.

L28 ANSWER 4 OF 30 PASCAL COPYRIGHT 2005 INIST-CNRS. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2004-0584813 PASCAL
COPYRIGHT NOTICE: Copyright .COPYRGT. 2004 INIST-CNRS. All rights reserved.
TITLE (IN ENGLISH): Evaluation of **cysteine** proteases of **Plasmodium** vivax as antimalarial drug targets: sequence analysis and sensitivity to **cysteine** protease inhibitors
AUTHOR: NA Byoung-Kuk; KIM Tong-Soo; ROSENTHAL Philip J.; LEE Jong-Koo; KONG Yoon

CORPORATE SOURCE: Department of Molecular Parasitology and Center for Molecular Medicine, Sungkyunkwan University School of Medicine and Samsung Biomedical Research Institute, Suwon 440-746, Korea, Republic of; Department of Tropical and Endemic Parasitic Diseases, National Institute of Health, Seoul 122-701, Korea, Republic of; Department of Medicine, San Francisco General Hospital, University of California, San Francisco, CA, 94143-0811, United States; Bureau of Health Promotion, Ministry of Health and Welfare, Gwacheon 427-721, Korea, Republic of
SOURCE: Parasitology research : (1987), (2004), 94(4), 312-317, 16 refs.
ISSN: 0932-0113 CODEN: PARREZ
DOCUMENT TYPE: Journal
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: Germany, Federal Republic of
LANGUAGE: English
AVAILABILITY: INIST-5859, 354000120484280100
AN 2004-0584813 PASCAL
CP Copyright .COPYRGT. 2004 INIST-CNRS. All rights reserved.
AB **Cysteine** proteases perform critical roles in the life cycles of **malaria** parasites. In **Plasmodium** falciparum, **treatment** of **cysteine** protease inhibitors inhibits hemoglobin hydrolysis and blocks the parasite development in vitro and in vivo, suggesting that plasmodial cysteine proteases may be interesting targets for new chemotherapeutics. To determine whether sequence diversity may limit chemotherapy against **Plasmodium** vivax, we analyzed sequence variations in the genes encoding three **cysteine** proteases, vivapain-1, -2 and -3, in 22 wild isolates of P. vivax. The sequences were highly conserved among wild isolates. A small number of substitutions leading to amino acid changes were found, while they did not modify essential residues for the function or structure of the enzymes. The substrate specificities and sensitivities to synthetic cysteine protease inhibitors of vivapain-2 and -3 from wild isolates were also very similar. These results support the suggestion that cysteine proteases of P. vivax are promising antimalarial chemotherapeutic targets.

L28 ANSWER 5 OF 30 PASCAL COPYRIGHT 2005 INIST-CNRS. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2004-0091717 PASCAL
COPYRIGHT NOTICE: Copyright .COPYRGT. 2004 INIST-CNRS. All rights reserved.
TITLE (IN ENGLISH): Antimalarial activities of novel synthetic cysteine protease inhibitors
AUTHOR: LEE Belinda J.; SINGH Ajay; CHIANG Peggy; KEMP Scott J.; GOLDMAN Erick A.; WEINHOUSE Michael I.; VLASUK George P.; ROSENTHAL Philip J.
CORPORATE SOURCE: Department of Medicine, San Francisco General Hospital, University of California, San Francisco, San Francisco, United States; Corvas International San Diego, California, United States
SOURCE: Antimicrobial agents and chemotherapy, (2003), 47(12), 3810-3814, 20 refs.
ISSN: 0066-4804 CODEN: AACHAX
DOCUMENT TYPE: Journal
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United States
LANGUAGE: English
AVAILABILITY: INIST-13334, 354000118842520250
AN 2004-0091717 PASCAL
CP Copyright .COPYRGT. 2004 INIST-CNRS. All rights reserved.
AB Among promising new targets for antimalarial chemotherapy are the cysteine protease hemoglobinases falcipain-2 and falcipain-3. We evaluated the activities of synthetic peptidyl aldehyde and α-ketoamide **cysteine** protease inhibitors against these proteases, against cultured **Plasmodium** falciparum parasites,

and in a murine **malaria** model. Optimized compounds inhibited falcipain-2 and falcipain-3, blocked hemoglobin hydrolysis, and prevented the development of P. falciparum at nanomolar concentrations. The compounds were equally active against multiple strains of P. falciparum with varied sensitivities to standard antimalarial agents. The peptidyl inhibitors were consistently less active against vinckepain-2, the putative falcipain-2 and falcipain-3 ortholog of the rodent malaria parasite Plasmodium vinckei. The lead compound morpholinocarbonyl-leucine-homophenylalanine aldehyde, which blocked P. falciparum development at low nanomolar concentrations, was tested in a murine P. vinckei model. When infused continuously at a rate of 30 mg/kg of body weight/day, the compound delayed the progression of **malaria** but did not eradicate infections. Our data demonstrate the potent antimalarial activities of novel **cysteine** protease inhibitors. Additionally, they highlight the importance of consideration of the specific enzyme targets of animal model parasites. In the case of falcipains, differences between P. falciparum and rodent parasites complicate the use of the rodent malaria model in the drug discovery process.

L28 ANSWER 6 OF 30 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN DUPLICATE

ACCESSION NUMBER: 2003:37083280 BIOTECHNO
TITLE: In vivo gene silencing in Plasmodium berghei - A mouse malaria model
AUTHOR: Mohmmed A.; Dasaradhi P.V.N.; Bhatnagar R.K.; Chauhan V.S.; Malhotra P.
CORPORATE SOURCE: P. Malhotra, Intl. Ctr. for Genetic Eng./Biotech., Aruna Asaf Ali Marg, New Delhi 110 067, India. E-mail: pawanm@icgeb.res.in
SOURCE: Biochemical and Biophysical Research Communications, (26 SEP 2003), 309/3 (506-511), 28 reference(s) CODEN: BBRCA0 ISSN: 0006-291X
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 2003:37083280 BIOTECHNO
AB RNA interference (RNAi) has emerged as a specific and efficient tool to silence gene expression in a variety of organisms and cell lines. An important prospect for RNAi technology is its possible application in the **treatment** of diseases using short interfering RNAs (siRNAs). However, the effect of siRNAs in adult animals and their potential to **treat** or prevent diseases are yet to be fully investigated. The main goal of the present study is to find out whether it was possible to carry out RNAi on circulating **malaria** parasite in vivo. To trigger RNAi in mouse **malaria** parasite, we used siRNAs corresponding to **cysteine** protease genes of **Plasmodium** berghei (berghepain-1 & 2). Intravenous injections of berghepains' siRNAs in infected animal resulted in characteristic enlargement of food vacuole in circulating parasites. Protein analysis of these treated parasites showed substantial accumulation of hemoglobin, which is reminiscent of the effect observed upon treating **Plasmodium** falciparum with different **cysteine** protease inhibitors. Parasites treated with berghepain 1 & 2 siRNAs showed marked reduction in the levels of their cognate mRNAs, thereby suggesting specific inhibition of berghepains' gene expression in vivo. We also observed the generation of .apprx.25nt RNA species from berghepains' mRNAs in the treated parasites, which is a characteristic of an RNAi phenomenon. These results thus provide evidence that beyond its value for validation of gene functions, RNAi may provide a new approach for disease therapy. .COPYRGT. 2003 Elsevier Inc. All rights reserved.

L28 ANSWER 7 OF 30 LIFESCI COPYRIGHT 2005 CSA on STN DUPLICATE 2

ACCESSION NUMBER: 2003:108434 LIFESCI
TITLE: Influence of Chloroquine **Treatment** and Plasmodium falciparum Malaria Infection on Some Enzymatic and Non-enzymatic Antioxidant Defense Indices in Humans
AUTHOR: Olatunde Farombi, E.; Shyntum, Y.Y.; Emerole, G.O.

CORPORATE SOURCE: Department of Biochemistry, University of Ibadan, Nigeria; E-mail: olatunde_farombi@hotmail.com
SOURCE: Drug and Chemical Toxicology [Drug Chem. Toxicol.], (20030000) vol. 26, no. 1, pp. 59-71. ISSN: 0148-0545.
DOCUMENT TYPE: Journal
FILE SEGMENT: K
LANGUAGE: English
SUMMARY LANGUAGE: English

AB It is known that malaria infection is accompanied by increased production of reactive oxygen species (ROS) and that malaria parasites are sensitive to oxidative damage. This has been proved by the efficacy of some antimalarial drugs that are known to act via generation of ROS when administered clinically or experimentally. There is lack of information on the effect of chloroquine on the antioxidant defense systems of normal and malaria infected humans. Since chloroquine has remained the mainstay of therapeutic regimen in malaria endemic zones, the present investigation was therefore undertaken to study the status of blood antioxidant defense mechanism, and oxidative stress following chloroquine **treatment** in normal and plasmodium infected humans. Ten healthy persons (5 males and 5 females) with the same age range (18-35 years) were taken as control group. Ten other individuals were treated with 25 mg/kg body with chloroquine over three days. Ten patients with malaria, not under antimalarial therapy were taken as another group, while another set of 10 patients with malaria were treated with 25 mg/kg body weight over three days. The activity of superoxide dismutase was increased by 23% in individuals treated with chloroquine compared to controls while the activity of the enzyme decreased by 26% in malaria patients and by 43% in **malaria** patients treated with chloroquine. In all the **treatment** groups, the activities of catalase and **glutathione** peroxidase were lowered ($P<0.001$). Similarly the levels of vitamins A, C, and beta -carotene were decreased in the **treatment** groups while plasma ceruloplasmin was increased in the groups. Glutathione and cholesterol levels were decreased while malondialdehyde level was increased significantly. Chloroquine **treatment** mediated oxidative stress in the host and this effect was exacerbated in Plasmodium falciparum infected patients administered with the drug.

L28 ANSWER 8 OF 30 LIFESCI COPYRIGHT 2005 CSA on STN
ACCESSION NUMBER: 2003:75816 LIFESCI
TITLE: The **treatment** of Plasmodium falciparum-infected erythrocytes with chloroquine leads to accumulation of ferriprotoporphyrin IX bound to particular parasite proteins and to the inhibition of the parasite's 6-phosphogluconate dehydrogenase
AUTHOR: Famin, O.; Ginsburg, H.
CORPORATE SOURCE: Department of Biological Chemistry, Institute of Life Sciences, The Hebrew University of Jerusalem, Jerusalem 91904, Israel; E-mail: hagai@vms.huji.ac.il
SOURCE: Parasite, (20030300) vol. 10, no. 1, pp. 39-50. ISSN: 1252-607X.
DOCUMENT TYPE: Journal
FILE SEGMENT: K
LANGUAGE: English
SUMMARY LANGUAGE: English; French

AB Ferriprotoporphyrin IX (FPIX) is a potentially toxic product of hemoglobin digestion by intra-erythrocytic **malaria** parasites. It is detoxified by biomineralization or through degradation by **glutathione**. Both processes are inhibited by the antimalarial drug chloroquine, leading to the accumulation of FPIX in the membranes of the infected cell and their consequent permeabilization. It is shown here that **treatment** of Plasmodium falciparum-infected erythrocytes with chloroquine also leads to the binding of FPIX to a subset of parasite proteins. Parasite enzymes such as aldolase, pyrimidine nucleoside monophosphate kinase and pyrimidine 5'-nucleotidase were inhibited by FPIX in vitro, but only the activity of 6-phosphogluconate dehydrogenase was reduced significantly in cells after drug **treatment**. Additional

proteins were extracted from parasite cytosol by their ability to bind FPIX. Sequencing of these proteins identified heat shock proteins 90 and 70, enolase, elongation factor 1- alpha , phosphoglycerate kinase, glyceraldehyde 3-phosphate dehydrogenase, L-lactate dehydrogenase and gametocytogenesis onset-specific protein. The possible involvement of these proteins in the antimalarial mode of action of chloroquine is discussed. It is concluded that drug-induced binding of FPIX to parasite glycolytic enzymes could underlie the demonstrable inhibition of glycolysis by chloroquine. The inhibition of 6-phosphogluconate dehydrogenase could explain the reduction of the activity of the hexose monophosphate shunt by the drug. Inhibition of both processes is deleterious to parasite survival. Binding of FPIX to other proteins is probably inconsequential to the rapid killing of the parasite by chloroquine.

L28 ANSWER 9 OF 30 LIFESCI COPYRIGHT 2005 CSA on STN DUPLICATE 3
ACCESSION NUMBER: 2002:105824 LIFESCI
TITLE: **Cysteine** Proteases of **Malaria** Parasites: Targets for Chemotherapy
AUTHOR: Rosenthal, P.J.; Sijwali, P.S.; Singh, A.; Shenai, B.R.
CORPORATE SOURCE: Box 0811, University of California, San Francisco, CA 94143-0811 USA; E-mail: rosnthl@itsa.ucsf.edu
SOURCE: Current Pharmaceutical Design [Curr. Pharm. Des.], (20020000) vol. 8, no. 18, pp. 1659-1672. ISSN: 1381-6128.
DOCUMENT TYPE: Journal
TREATMENT CODE: General Review
FILE SEGMENT: K
LANGUAGE: English
SUMMARY LANGUAGE: English
AB New drugs to **treat malaria** are urgently needed. **Cysteine** proteases of **malaria** parasites offer potential new chemotherapeutic targets. **Cysteine** protease inhibitors block parasite hemoglobin hydrolysis and development, indicating that cysteine proteases play a key role in hemoglobin degradation, a necessary function of erythrocytic trophozoites. These inhibitors also block the rupture of erythrocytes by mature parasites, suggesting an additional role for cysteine proteases in the hydrolysis of erythrocyte cytoskeletal proteins. Recent studies have shown that the repertoire of **cysteine** proteases of **malaria** parasites is larger than was previously realized. **Plasmodium** falciparum, the most virulent human **malaria** parasite, expresses three papain-family **cysteine** proteases, known as falcipains. All three proteases are expressed by trophozoites and hydrolyze hemoglobin at acidic pH, suggesting roles in this process. Falcipain-2 also hydrolyzes ankyrin at neutral pH, suggesting additional activity against erythrocyte cytoskeletal targets. Multiple orthologs of the falcipains have been identified in other plasmodial species. Analysis of orthologs from animal model rodent parasites identified similar features, but some noteworthy biochemical differences between the cysteine proteases. These differences must be taken into account in interpreting in vivo experiments. A number of small molecule cysteine protease inhibitors blocked parasite hemoglobin hydrolysis and development, and inhibitory effects against parasites generally correlated with inhibition of falcipain-2. Some compounds also cured mice infected with otherwise lethal malaria infections. Current research priorities are to better characterize the biological roles and biochemical features of the falcipains. In addition, efforts to identify optimal falcipain inhibitors as antimalarials are underway.

L28 ANSWER 10 OF 30 PASCAL COPYRIGHT 2005 INIST-CNRS. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2002-0599218 PASCAL
COPYRIGHT NOTICE: Copyright .COPYRGT. 2002 INIST-CNRS. All rights reserved.
TITLE (IN ENGLISH): A prodrug form of a **Plasmodium** falciparum **glutathione** reductase inhibitor conjugated with a 4-anilinoquinoline
AUTHOR: DAVIOUD-CHARVET Elisabeth; DELARUE Sandrine; BIOT

Christophe; SCHWOEBEL Babett; BOEHME Catharina C.; MUESSIGBRODT Andreas; MAES Louis; SERGHERAERT Christian; GRELLIER Philippe; SCHIRMER R. Heiner; BECKER Katia
SOURCE: Journal of medicinal chemistry : (Print), (2001), 44(24), 4268-4276, 53 refs.
ISSN: 0022-2623 CODEN: JMCMAR
DOCUMENT TYPE: Journal
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United States
LANGUAGE: English
AVAILABILITY: INIST-9165, 354000099347050240
AN 2002-0599218 PASCAL

AB **Glutathione** (GSH), which is known to guard **Plasmodium** falciparum from oxidative damage, may have an additional protective role by promoting heme catabolism. An elevation of GSH content in parasites leads to increased resistance to chloroquine (CQ), while GSH depletion in resistant P. falciparum strains is expected to restore the sensitivity to CQ. High intracellular GSH levels depend inter alia on the efficient reduction of GSSG by glutathione reductase (GR). On the basis of this hypothesis, we have developed a new strategy for overcoming glutathione-dependent 4-aminoquinoline resistance. To direct both a 4-aminoquinoline and a GR inhibitor to the parasite, double-drugs were designed and synthesized. Quinoline-based alcohols (with known antimalarial activity) were combined with a GR inhibitor via a metabolically labile ester bond to give double-headed prodrugs. The biochemically most active double-drug 7 of this series was then evaluated as a growth inhibitor against six Plasmodium falciparum strains that differed in their degree of resistance to CQ; the ED.sub.5.sub.0 values for CQ ranged from 14 to 183 nM. While the inhibitory activity of the original 4-aminoquinoline-based alcohol followed that of CQ in these tests, the double-drug exhibited similar efficiency against all strains, the ED.sub.5.sub.0 being as low as 28 nM. For the ester 7, a dose-dependent decrease in glutathione content and GR activity and an increase in glutathione-S-transferase activity were determined in treated parasites. The drug was subsequently tested for its antimalarial action in vivo using murine malaria models infected with P. berghei. A 178% excess mean survival time was determined for the animals treated with 40 mg/kg 7 for 4 days. No cytotoxicity due to this compound was observed. Work is in progress to extend and validate the strategy outlined here.

L28 ANSWER 11 OF 30 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
DUPLICATE
ACCESSION NUMBER: 2001:32095899 BIOTECHNO
TITLE: Malaria parasite exit from the host erythrocyte: A two-step process requiring extraerythrocytic proteolysis
AUTHOR: Salmon B.L.; Oksman A.; Goldberg D.E.
CORPORATE SOURCE: D.E. Goldberg, Howard Hughes Medical Institute, Dept. of Molec. Med./Microbiology, Washington University School of Med., St. Louis, MO 63110, United States. E-mail: goldberg@borcim.wustl.edu
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (02 JAN 2001), 98/1 (271-276), 18 reference(s)
CODEN: PNASA6 ISSN: 0027-8424
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 2001:32095899 BIOTECHNO
AB Intraerythrocytic malaria parasites replicate by the process of schizogeny, during which time they copy their genetic material and package it into infective merozoites. These merozoites must then exit the host cell to invade new erythrocytes. To better characterize the events of merozoite escape, erythrocytes containing **Plasmodium** falciparum schizonts were cultured in the presence of the

cysteine protease inhibitor, L-transepoxy-succinyl-leucylamido-(4-guanidino)butane (E64). This **treatment** resulted in the accumulation of extraerythrocytic merozoites locked within a thin, transparent membrane. Immunomicroscopy demonstrated that the single membrane surrounding the merozoites is not erythrocytic but rather is derived from the parasitophorous vacuolar membrane (PVM). Importantly, structures identical in appearance can be detected in untreated cultures at low frequency. Further studies revealed that (i) merozoites from the PVM-enclosed merozoite structures (PEMS) are invasive, viable, and capable of normal development; (ii) PEMS can be purified easily and efficiently; and (iii) when PEMS are added to uninfected red blood cells, released merozoites can establish a synchronous wave of infection. These observations suggest that L-transepoxy-succinyl-leucylamido-(4-guanidino)butane (E64) causes an accumulation of an intermediate normally present during the process of rupture. We propose a model for the process of rupture: merozoites enclosed within the PVM first exit from the host erythrocyte and then rapidly escape from the PVM by a proteolysis-dependent mechanism.

L28 ANSWER 12 OF 30 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
DUPLICATE

ACCESSION NUMBER: 2000:30845527 BIOTECHNO
TITLE: A **cysteine** protease activity from **Plasmodium** falciparum cleaves human erythrocyte ankyrin
AUTHOR: Raphael P.; Takakuwa Y.; Manno S.; Liu S.-C.; Chishti A.H.; Hanspal M.
CORPORATE SOURCE: M. Hanspal, Division of Hematology Research, Department of Medicine, Tufts University School of Medicine, Boston, MA 02135, United States. E-mail: mhanspal@semc.org
SOURCE: Molecular and Biochemical Parasitology, (2000), 110/2 (259-272), 48 reference(s)
CODEN: MBIPDP ISSN: 0166-6851
PUBLISHER ITEM IDENT.: S0166685100002838
DOCUMENT TYPE: Journal; Article
COUNTRY: Netherlands
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 2000:30845527 BIOTECHNO
AB The malaria parasite Plasmodium falciparum undergoes distinct morphologic changes during its 48-h life cycle inside human red blood cells. Parasite proteinases appear to play important roles at all stages of the erythrocytic cycle of human malaria. Proteases involved in erythrocyte rupture and invasion are possibly required to breakdown erythrocyte membrane skeleton. To identify such proteases, soluble cytosolic extract of isolated trophozoites/schizonts was incubated with erythrocyte membrane ghosts or spectrin-actin depleted inside-out vesicles, which were then analyzed by SDS-PAGE. In both cases, a new protein band of 155 kDa was detected. The N-terminal peptide sequencing established that the 155 kDa band represents truncated ankyrin. Immunoblot analysis using defined monoclonal antibodies confirmed that ankyrin was cleaved at the C-terminus. While the enzyme preferentially cleaved ankyrin, degradation of protein 4.1 was also observed at high concentrations of the enzyme. The optimal activity of the purified enzyme, using ankyrin as substrate, was observed at pH 7.0-7.5, and the activity was strongly inhibited by standard inhibitors of cysteine proteinases (cystatin, NEM, leupeptin, E-64 and MDL 28 170), but not by inhibitors of aspartic (pepstatin) or serine (PMSF, DFP) proteinases. Furthermore, we demonstrate that protease digestion of ankyrin substantially reduces its interaction with ankyrin-depleted membrane vesicles. Ektacytometric measurements showed a dramatic increase in the rate of fragmentation of ghosts after **treatment** with the protease. Although the role of ankyrin cleavage in vivo remains to be determined, based on our findings we postulate that the parasite-derived cysteine protease activity cleaves host ankyrin thus weakening the ankyrin-band 3 binding interactions and destabilizing the erythrocyte membrane skeleton, which, in turn, facilitates parasite release. Further characterization of the enzyme may

lead to the development of novel antimalarial drugs. (C) 2000 Elsevier Science B.V.

L28 ANSWER 13 OF 30 PASCAL COPYRIGHT 2005 INIST-CNRS. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2000-0407358 PASCAL
COPYRIGHT NOTICE: Copyright .COPYRGT. 2000 INIST-CNRS. All rights reserved.
TITLE (IN ENGLISH): **Arginine** vasopressin secretion in Kenyan children with severe **malaria**
AUTHOR: SOWUNMI A.; NEWTON C. R. J. C.; WARUIRU C.; LIGHTMAN S.; DUNGER D. B.
CORPORATE SOURCE: Centre for Geographical Medicine (Coast), Kenya Medical Research Institute, Kilifi, Kenya; Department of Pharmacology and Therapeutics, University of Ibadan, Nigeria; Institute of Child Health, London, United Kingdom; Department of Medicine, University of Bristol, United Kingdom; Department of Paediatrics, Oxford University, Oxford, United Kingdom
SOURCE: Journal of tropical pediatrics : (1980), (2000), 46(4), 195-199, 18 refs.
ISSN: 0142-6338 CODEN: JTRPAO
DOCUMENT TYPE: Journal
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United Kingdom
LANGUAGE: English
AVAILABILITY: INIST-10240, 354000090828280010
AN 2000-0407358 PASCAL
CP Copyright .COPYRGT. 2000 INIST-CNRS. All rights reserved.
AB Hyponatraemia is common in African children with severe **malaria**, but the cause is unknown. We measured plasma sodium (p[Na]) and **arginine** vasopressin concentrations (p[AVP]) in 30 consecutive children with severe **malaria** (19 had cerebral **malaria**), on admission, at 48 and 96h after admission. Hyponatraemia (p[Na] <130 mmol/l) occurred in 53 per cent of the children and was unrelated to peripheral parasite density, dehydration or abnormal renal function. The highest p[AVP] were seen in patients with cerebral malaria. Overall, p[AVP] declined 96 h after **treatment**. In children with hyponatraemia (cerebral and non-cerebral), p[AVP] levels were not suppressed and in 67 per cent of cases they were deemed inappropriate. Inappropriate AVP secretion is common in children with severe malaria and may influence fluid therapy after correction of initial dehydration.

L28 ANSWER 14 OF 30 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN DUPLICATE

ACCESSION NUMBER: 2000:30827223 BIOTECHNO
TITLE: The Toxoplasma homolog of Plasmodium apical membrane antigen-1 (AMA-1) is a microneme protein secreted in response to elevated intracellular calcium levels
AUTHOR: Donahue C.G.; Carruthers V.B.; Gilk S.D.; Ward G.E.
CORPORATE SOURCE: G.E. Ward, Department of Microbiology, 214 Stafford Hall, University of Vermont, Burlington, VT 05405, United States.
E-mail: gward@zoo.uvm.edu
SOURCE: Molecular and Biochemical Parasitology, (2000), 111/1 (15-30), 44 reference(s)
CODEN: MBIPDP ISSN: 0166-6851
PUBLISHER ITEM IDENT.: S0166685100002899
DOCUMENT TYPE: Journal; Article
COUNTRY: Netherlands
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 2000:30827223 BIOTECHNO
AB A monoclonal antibody (MAb) has been generated against a novel 63 kDa surface/apical antigen of Toxoplasma gondii tachyzoites which is identified here as TgAMA-1, the Toxoplasma homolog of Plasmodium apical membrane antigen-1 (AMA-1). Sequence analysis, phase partitioning in Triton X-114, and labeling of TgAMA-1 with iodonaphthalene azide all

suggest that TgAMA-1 is a type I transmembrane protein. There is a high degree of sequence similarity between TgAMA-1 and **Plasmodium** AMA-1, most notably in the position of conserved **cysteine** residues within the protein's predicted extracellular domain. In contrast to full length **Plasmodium** AMA-1, which has previously been localized to the rhoptries, it is shown here by immunofluorescence and immunoelectron microscopy that intracellular TgAMA-1 is found in the micronemes. A 53 kDa N-terminal proteolytic fragment of TgAMA-1 is constitutively secreted from the parasite at 37°C. As is the case with other microneme proteins, the proteolytic processing and secretion of TgAMA-1 is dramatically enhanced in response to **treatments** which increase intracellular calcium levels. Copyright (C) 2000 Elsevier Science B.V.

L28 ANSWER 15 OF 30 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 1999:29150307 BIOTECHNO
TITLE: Cysteine protease inhibitors as chemotherapy for parasitic infections
AUTHOR: McKerrow J.H.; Engel J.C.; Caffrey C.R.
CORPORATE SOURCE: J.H. McKerrow, Department of Pathology, VA Medical Center-113B, University of California, 4150 Clement Street, San Francisco, CA 94121, United States. E-mail: jmck@cgl.ucsf.edu
SOURCE: Bioorganic and Medicinal Chemistry, (1999), 7/4 (639-644), 49 reference(s)
CODEN: BMECEP ISSN: 0968-0896
PUBLISHER ITEM IDENT.: S0968089699000085
DOCUMENT TYPE: Journal; Article
COUNTRY: United Kingdom
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1999:29150307 BIOTECHNO
AB Analysis of the evolution, localization and biologic function of papain family cysteine proteases in metazoan and protozoan parasites has provided important and often surprising insights into the biochemistry and cellular function of this diverse enzyme family. Furthermore, the relative lack of redundancy of cysteine proteases in parasites compared to their mammalian hosts makes them attractive targets for the development of new antiparasitic chemotherapy. The **treatment** of experimental models of parasitic diseases with cysteine protease inhibitors has provided an important 'proof of concept' for the use of cysteine protease inhibitors in vivo. Evidence has now accumulated that cysteine protease inhibitors can selectively arrest replication of a microbial pathogen without untoward toxicity to the host. Furthermore, this can be achieved with reasonable dosing schedules and oral **administration** of the drug. Initial studies have confirmed the efficacy of **cysteine** protease inhibitors in **treatment** of Trypanosoma cruzi, **Plasmodium** falciparum and Leishmania major. Work on Trypanosoma brucei, the agent of African trypanosomiasis, is preliminary but also promising. Target validation studies have shown that biotinylated or radiolabeled irreversible inhibitors specifically bind to the cysteine protease targets thought to represent the major activity within the parasite. In the case of T. cruzi, the effect of inhibitors appears to be predominantly in blocking protease processing. Transfection studies using variant constructs have supported this model. Finally, the generation of null mutants for the multiple protease genes in Leishmania mexicana has provided the first genetic support for the key role of this enzyme family in parasite virulence. Safety studies in rodents and analysis of uptake of inhibitors by parasites and host cells suggest that the selectivity of inhibitors for the parasite targets may reside in the lack of redundancy of parasite proteases, the higher concentration of host proteases in intracellular compartments, and differential uptake of inhibitors by parasites. Attempts to elicit resistance to cysteine protease inhibitors in parasite cultures suggest that mechanisms of induced resistance are independent of resistance to the traditional antiparasitic agents. This suggests that cysteine protease inhibitors may provide an alternative to traditional therapy in drug-resistant organisms. Copyright (C) 1999 Elsevier Science Ltd.

L28 ANSWER 16 OF 30 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 1999:29150306 BIOTECHNO
TITLE: Antimalarial effects in mice of orally administered peptidyl cysteine protease inhibitors
AUTHOR: Olson J.E.; Lee G.K.; Semenov A.; Rosenthal P.J.
CORPORATE SOURCE: P.J. Rosenthal, Department of Medicine, San Francisco General Hospital, University of California, San Francisco, CA 94143, United States.
E-mail: rosnthl@itsa.ucsf.edu
SOURCE: Bioorganic and Medicinal Chemistry, (1999), 7/4 (633-638), 28 reference(s)
CODEN: BMECEP ISSN: 0968-0896
PUBLISHER ITEM IDENT.: S0968089699000048
DOCUMENT TYPE: Journal; Conference Article
COUNTRY: United Kingdom
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1999:29150306 BIOTECHNO
AB The **Plasmodium** falciparum **cysteine** protease falcipain is required for the degradation of hemoglobin by erythrocytic **malaria** parasites. In prior studies, peptidyl inhibitors of falcipain blocked hemoglobin degradation and development by cultured parasites and one of these compounds, when administered parenterally, cured Plasmodium vinckei-infected mice. We now report an evaluation of orally administered peptidyl inhibitors of falcipain in a mouse malaria model. In studies with a fluoromethyl ketone, orally administered morpholine urea-phenylalanine-homophenylalanine-fluoromethyl ketone delayed the progression of murine malaria. In studies of a new series of vinyl sulfones, a set of related compounds demonstrated marked inhibition of falcipain and of parasite biological activities in vitro. One of these compounds, N-methyl piperazine urea-leucine-homophenylalanine-2-naphthalene vinyl sulfone, cured about 40% of mice when administered orally twice-a-day for four days. Our results suggest that peptidyl inhibitors of falcipain have promise as antimalarial chemotherapeutic agents. Copyright (C) 1999 Elsevier Science Ltd.

L28 ANSWER 17 OF 30 PASCAL COPYRIGHT 2005 INIST-CNRS. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 1999-0429805 PASCAL
COPYRIGHT NOTICE: Copyright .COPYRGT. 1999 INIST-CNRS. All rights reserved.
TITLE (IN ENGLISH): Use of reconstituted influenza virus virosomes as an immunopotentiating delivery system for a peptide-based vaccine
AUTHOR: POELTL-FRANK F.; ZURBRIGGEN R.; HELG A.; STUART F.; ROBINSON J.; GLUECK R.; PLUSCHKE G.
CORPORATE SOURCE: Swiss Tropical Institute, Basel, Switzerland; Swiss Serum and Vaccine Institute, Bern, Switzerland; Institute of Organic Chemistry, University of Zuerich, Zuerich, Switzerland
SOURCE: Clinical and experimental immunology, (1999), 117(3), 496-503, 30 refs.
ISSN: 0009-9104 CODEN: CEXIAL
DOCUMENT TYPE: Journal
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United Kingdom
LANGUAGE: English
AVAILABILITY: INIST-12690, 354000085900860130
AN 1999-0429805 PASCAL
CP Copyright .COPYRGT. 1999 INIST-CNRS. All rights reserved.
AB Immunopotentiating reconstituted influenza virosomes (IRIV) were used as a delivery system for the synthetic peptide-based **malaria** vaccine SPf66. The reduced SPf66 peptide molecules containing terminal **cysteine** residues were covalently attached to phosphatidylethanolamine with the heterobifunctional crosslinker γ-maleimidobutyric acid N-hydroxysuccinimide ester. The SPf66-phosphatidylethanolamine was incorporated into IRIV and BALB/c mice

were immunized twice by intramuscular injection with peptide-loaded virosomes. Titres of elicited anti-SPf66 IgG were determined by ELISA. These titres were significantly higher and the required doses of antigen were lower, when mice had been preimmunized with a commercial whole virus influenza vaccine. After pre-immunization with the influenza vaccine, SPf66-IRIV elicited far more consistently anti-SPf66 antibody responses than SPf(66).sub.n adsorbed to alum. MoAb produced by four B cell hybridoma clones derived from a SPf66-IRIV-immunized mouse cross-reacted with Plasmodium falciparum blood stage parasites in immunofluorescence assays. All four MoAbs were specific for the merozoite surface protein- 1 (MSP-1)-derived 83.1 portion of SPf66. Sequencing of their functionally rearranged K light chain variable region genes demonstrated that the four hybridomas were generated from clonally related splenic B cells. Biomolecular interaction analyses (BIA) together with these sequencing data provided evidence for the selection of somatically mutated affinity-matured B cells upon repeated immunization with SPf66-IRIV. The results indicate that IRIV are a suitable delivery system for synthetic peptide vaccines and thus have a great potential for the design of molecularly defined combined vaccines targeted against multiple antigens and development stages of one parasite, as well as against multiple pathogens.

L28 ANSWER 18 OF 30 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
DUPLICATE
ACCESSION NUMBER: 1999:29076734 BIOTECHNO
TITLE: Role of **glutathione** in the detoxification of ferriprotoporphyrin IX in chloroquine resistant **Plasmodium** berghei
AUTHOR: Platel D.F.N.; Mangou F.; Tribouley-Duret J.
CORPORATE SOURCE: D.F.N. Platel, Laboratoire Biochimie, Institut Bergonie, 180 Rue St-Genes, 33076 Bordeaux Cedex, France.
E-mail: denis.patel@cancero.u-bordeaux2.fr
SOURCE: Molecular and Biochemical Parasitology, (1999), 98/2 (215-223), 37 reference(s)
CODEN: MBIPDP ISSN: 0166-6851
PUBLISHER ITEM IDENT.: S0166685198001704
DOCUMENT TYPE: Journal; Article
COUNTRY: Netherlands
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1999:29076734 BIOTECHNO
AB The reduction in hemozoin content is a well known feature of chloroquine-resistant Plasmodium berghei. Using NK65-derived lines displaying increasing resistance levels, we observed an inverse relationship between the hemozoin content, and the glutathione (GSH) and glutathione S-transferase (GST) levels. **Treatment** of highly chloroquine-resistant-infected mice with buthionine sulfoximine (BSO), which has previously been shown to partially reverse this chloroquine resistance, led to a significant increase in hemozoin production. In vitro studies on the polymerization of ferriprotoporphirin IX (FPIX) at pH 5.0 showed that GSH partially inhibited β-hematin synthesis, while GST had a trivial and non specific effect. Furthermore, chloroquine-sensitive parasites invading reticulocytes displayed higher GSH level and GST activity, and reduced hemozoin synthesis and susceptibility to chloroquine. We conclude that, in chloroquine resistant P. berghei, GSH can detoxify hemin within the food vacuole, thus precluding its polymerization and preventing the activity of chloroquine and other quinoline-containing drugs. It is proposed that vacuolar GSH could be ascribed to an erythrocytic origin, since the resistant lines invade reticulocytes, which contain higher levels of GSH and GST than normocytes. Copyright (C) 1999 Elsevier Science Ireland Ltd.

L28 ANSWER 19 OF 30 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 1998:28469003 BIOTECHNO
TITLE: Comparison of humoral immune responses elicited by DNA and protein vaccines based on merozoite surface protein-1 from Plasmodium yoelii, a rodent malaria

parasite
AUTHOR: Kang Y.; Calvo P.A.; Daly T.M.; Long C.A.
CORPORATE SOURCE: Dr. C.A. Long, Dept. of Microbiology and Immunology, Allegheny Univ. of Health Sciences, 2900 Queen Lane, Philadelphia, PA 19129, United States.
SOURCE: Journal of Immunology, (15 OCT 1998), 161/8 (4211-4219), 59 reference(s)
CODEN: JOIMA3 ISSN: 0022-1767
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1998:28469003 BIOTECHNO
AB Immunization With DNA vaccines encoding relevant Ags can induce not only cell-mediated immune response but also humoral immune responses against pathogenic microorganisms in several animal models, Our previous results demonstrated that, when the C terminus (PyC2) of Plasmodium yoelii merozoite surface protein-1 (MSP-1), a leading vaccine candidate against erythrocytic stages of **malaria**, was expressed as a fusion protein (GST-PyC2) with **glutathione** S-transferase (GST), it elicited Ab-mediated protective immune responses in BALB/c mice. In our present study, we wished to examine the humoral responses to a DNA vaccine (V3) encoding GST-PyC2. The GST-PyC2 expressed in V3-transfected Cos 7 cells was recognized by a protective monoclonal Ab to PyC2 (mAb302), although the secreted product had undergone N-linked glycosylation. When BALB/c mice were immunized with V3 plasmid, anti-PyC2 Abs were successfully induced. These Abs immunoprecipitated native PyMSP-1 protein and competed with mAb302 for binding to its epitope at a level similar to those elicited by GST-PyC2 protein immunization. However, these Abs had significantly lower titers and avidities, and different isotype profiles and protective capacities against a lethal erythrocytic stage challenge, than those resulting from immunization with GST-PyC2 protein. Most surprising was the finding that, in contrast to protein immunization, there was no significant increase in the avidity of either GST-specific or PyC2- specific IgG Abs during the course of DNA immunization. This suggests that there may be little or no affinity maturation of specific Abs during DNA immunization in this system.

L28 ANSWER 20 OF 30 LIFESCI COPYRIGHT 2005 CSA on STN DUPLICATE 8
ACCESSION NUMBER: 1998:115043 LIFESCI
TITLE: Antimalarial synergy of cysteine and aspartic protease inhibitors
AUTHOR: Semenov, A.; Olson, J.E.; Rosenthal, Ph.J.*
CORPORATE SOURCE: Dept. of Medicine, Box 0811, University of California, San Francisco, CA 94143-0811, USA
SOURCE: Antimicrob. Agents Chemother., (19980900) vol. 42, no. 9, pp. 2254-2258.
ISSN: 0066-4804.
DOCUMENT TYPE: Journal
FILE SEGMENT: K
LANGUAGE: English
SUMMARY LANGUAGE: English
AB It has been proposed that the **Plasmodium** falciparum **cysteine** protease falcipain and aspartic proteases plasmepsin I and plasmepsin II act cooperatively to hydrolyze hemoglobin as a source of amino acids for erythrocytic parasites. Inhibitors of each of these proteases have potent antimalarial effects. We have now evaluated the antimalarial effects of combinations of cysteine and aspartic protease inhibitors. When incubated with cultured P. falciparum parasites, cysteine and aspartic protease inhibitors exhibited synergistic effects in blocking parasite metabolism and development. The inhibitors also demonstrated apparent synergistic inhibition of plasmodial hemoglobin degradation both in culture and in a murine **malaria** model. When evaluated for the **treatment** of murine **malaria**, a combination of **cysteine** and aspartic protease inhibitors was much more effective than higher concentrations of either compound used alone. These results support a model whereby plasmodial cysteine and aspartic proteases participate in the degradation of hemoglobin, and they suggest that

combination antimalarial therapy with inhibitors of the two classes of proteases is worthy of further study.

L28 ANSWER 21 OF 30 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 1998:28112556 BIOTECHNO
TITLE: Plasmodium falciparum polyoximes: Highly immunogenic synthetic vaccines constructed by chemoselective ligation of repeat B-cell epitopes and a universal T-cell epitope of CS protein
AUTHOR: Nardin E.H.; Calvo-Calle J.M.; Oliveira G.A.; Clavijo P.; Nussenzweig R.; Simon R.; Zeng W.; Rose K.
CORPORATE SOURCE: E.H. Nardin, Dept. Medical/Molecular Parasitology, New York University, School of Medicine, 341 East 25th Street, New York, NY 10010, United States.
E-mail: elizabeth.nardin@mcems.med.nyu.edu
SOURCE: Vaccine, (1998), 16/6 (590-600), 41 reference(s)
CODEN: VACCDE ISSN: 0264-410X
PUBLISHER ITEM IDENT.: S0264410X97002387
DOCUMENT TYPE: Journal; Article
COUNTRY: United Kingdom
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1998:28112556 BIOTECHNO
AB Effective immunoprophylaxis directed against the pre-erythrocytic stages of the malaria parasite requires a vaccine that can elicit humoral and cell mediated immunity in individuals of diverse genetic background. In order for a synthetic peptide malaria vaccine to meet these requirements, problems associated with genetic restriction, peptide chemistry, adjuvant formulation and physiochemical characterization of the final synthetic vaccine product must first be overcome. To address these issues, five polyoxime vaccine candidates have been constructed by ligating purified peptide epitopes of the P. falciparum CS protein to a branched template via oxime bonds. All five constructs, including two based on templates containing the synthetic adjuvant tripalmitoyl-S-glyceryl **cysteine** (Pam3Cys), were of sufficient purify for characterization by mass spectrometry. The immunogenicity of the **malaria** polyoximes in different murine strains was compared to that of multiple antigen peptide (MAP) constructs synthesized by standard step-wise synthesis. A tri-epitope polyoxime-Pam3Cys construct, based on the repeats and a universal T-cell epitope that contains both helper and CTL epitopes of the CS protein, was shown to be a precisely-defined synthetic malaria vaccine candidate that was highly immunogenic in murine strains of diverse H-2 haplotypes.

L28 ANSWER 22 OF 30 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
DUPLICATE
ACCESSION NUMBER: 1996:27062391 BIOTECHNO
TITLE: Characterization of native falcipain, an enzyme involved in Plasmodium falciparum hemoglobin degradation
AUTHOR: Francis S.E.; Gluzman I.Y.; Oksman A.; Banerjee D.; Goldberg D.E.
CORPORATE SOURCE: D.E. Goldberg, Washington Univ. School of Medicine, Box 8230, 660 S. Euclid Avenue, St. Louis, MO 63110, United States.
E-mail: goldberg@borim.wustl.edu
SOURCE: Molecular and Biochemical Parasitology, (1996), 83/2 (189-200), 48 reference(s)
CODEN: MBIPDP ISSN: 0166-6851
PUBLISHER ITEM IDENT.: S0166685196027727
DOCUMENT TYPE: Journal; Article
COUNTRY: Netherlands
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1996:27062391 BIOTECHNO
AB In **Plasmodium** falciparum, a **cysteine** protease known as falcipain has been implicated in the essential metabolic process of hemoglobin degradation. Parallel lines of investigation, using native or

recombinant enzyme, have led to differing conclusions about the specificity and role of this protease. We have now determined that (1) Native falcipain does not cleave hemoglobin unless this substrate has first been denatured by reducing agents, acid-acetone **treatment** or plasmepsin action. (2) Reducing agents such as glutathione cannot denature hemoglobin in the presence of catalase, which is accumulated in the digestive vacuole. (3) The purified native enzyme has kinetics similar to those obtained with trophozoite extract, but substantially different from those of recombinant enzyme. (4) Although there are numerous cysteine protease genes in the P. falciparum genome, the falcipain gene is the only one whose transcript can be detected in the early intraerythrocytic parasites. We conclude that falcipain likely works by degrading hemoglobin fragments after initial aspartic protease attack has denatured the substrate. We propose that falcipain inhibitors block the initial steps of degradation indirectly by promoting vacuolar accumulation of osmotically active hemoglobin peptides.

L28 ANSWER 23 OF 30 LIFESCI COPYRIGHT 2005 CSA on STN DUPLICATE 10
ACCESSION NUMBER: 97:45603 LIFESCI
TITLE: The heme moiety of malaria pigment (beta -hematin) mediates the inhibition of nitric oxide and tumor necrosis factor alpha production by lipopolysaccharide-stimulated macrophages
AUTHOR: Taramelli, D.; Basilico, N.; Pagani, E.; Grande, R.; Monti, D.; Ghione, M.; Olliaro, P.
CORPORATE SOURCE: Istituto di Microbiologia Medica, Univ. di Milano, Via Pascal 36, 20133 Milano, Italy
SOURCE: EXP. PARASITOL., (1995) vol. 81, no. 4, pp. 501-511. ISSN: 0014-4894.
DOCUMENT TYPE: Journal
FILE SEGMENT: K
LANGUAGE: English
SUMMARY LANGUAGE: English
AB To investigate the effect of the heme moiety of malaria pigment, hemozoin, on phagocyte functions, mouse macrophages were fed with insoluble beta -hematin, the synthetic heme-polymer chemically identical to the native pigment, or the soluble monomer, hematin. Production of inflammatory cytokines, interleukin 1 (IL1), tumor necrosis factor alpha (TNF alpha), and nitric oxide (NO) was assayed in the supernatants after stimulation with lipopolysaccharide. The results indicate that both beta -hematin and hematin induce a dose-dependent inhibition of macrophage production of TNF alpha and NO, but not of IL1. One-hour pretreatment with soluble hematin inhibited production of cytotoxic mediators by more than 50% compared to controls, while 6-hr exposure was necessary for insoluble beta -hematin to induce the same level of inhibition. However, the same **treatment** did not modify the production of TNF alpha and NO by mouse microglia cell lines. The inhibition was partially counterbalanced by adding sulphydryl group donors such as 2-mercaptoethanol, glutathione, or N-acetyl-**cysteine** during the preincubation time. The results of the present study confirm the inhibitory role of **malaria** pigment and show that such effect is due to the heme moiety and may be selective for the production of cytotoxic mediators by specific phagocytes. The implications of these findings in the control of malaria infection and disease and in the pathogenesis of severe malaria are discussed.

L28 ANSWER 24 OF 30 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 1995:25182163 BIOTECHNO
TITLE: Monopalmitic acid-peptide conjugates induce cytotoxic T cell responses against malarial epitopes: Importance of spacer amino acids
AUTHOR: Verheul A.F.M.; Udhayakumar V.; Jue D.L.; Wohlhueter R.M.; Lal A.A.
CORPORATE SOURCE: Division of Parasitic Diseases, National Centers for Infectious Dis., Ctrs. for Disease Control/Prevention, 1600 Clifton Road,Atlanta, GA 30333, United States.
SOURCE: Journal of Immunological Methods, (1995), 182/2 (219-226)

CODEN: JIMMBG ISSN: 0022-1759
DOCUMENT TYPE: Journal; Article
COUNTRY: Netherlands
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1995:25182163 BIOTECHNO
AB Cytolytic T cells (CTL) play a critical role in providing protection against the liver stage of malaria infection. Previous investigations have shown that induction of CTL against peptide or proteins can be achieved by attachment of lipids. In the present study, we used the **Plasmodium** berghei circumsporozoite protein CTL epitope (SYIPSAEKI (PL76)). This peptide with **cysteine**-serine (CS) as spacer amino acids was coupled to palmitic acid (PA). The same CTL epitope containing only an extra serine was linked to S-¢2,3-bis(palmitoyloxy)-(2-RS)-propyl!-N-palmitoyl-(R)-(tripam-C). Inbred mice ¢(BALB/c x C57BL/6)F1! were immunized intravenously with the lipopeptides. Both types of lipopeptides induced significant CTL responses after one injection. Immunization of the monopalmitic acid-peptide conjugate intraperitoneally emulsified in Freund's complete adjuvant also induced a significant CTL response, but the magnitude was lower as compared to the intravenous route. The major advantages of the use of the simple monopalmitic acid-peptide conjugates are: (i) low costs of the fatty acid; (ii) coupling of lipid to peptide can be performed using the peptide synthesizer during standard peptide synthesis, and (iii) standard peptide methodology can be used for purification. To investigate whether a spacer amino acid sequence between the actual CTL epitope and PA is required for induction of an optimal CTL response, we prepared monopalmitic acid-peptide conjugates with different spacer amino acids. A lipopeptide without a spacer amino acid and another one containing the CS spacer sequence both induced a CTL response, whereas a lipopeptide with a serine as spacer failed to induce CTL. These resutls indicate that the amino acid spacer sequences influence the immunological properties of the palmitic acid-peptide conjugates.

L28 ANSWER 25 OF 30 LIFESCI COPYRIGHT 2005 CSA on STN DUPLICATE 11
ACCESSION NUMBER: 95:101871 LIFESCI
TITLE: Status of hepatic **glutathione**-S-transferase(s) during **Plasmodium** berghei infection and chloroquine **treatment** in Mastomys natalensis
AUTHOR: Srivastava, P.; Arif, A.J.; Pandey, V.C.
CORPORATE SOURCE: Cent. Drug Res. Inst., Lucknow 226 001, India
SOURCE: INT. J. PARASITOL., (1995) vol. 25, no. 2, pp. 203-205. ISSN: 0020-7519.
DOCUMENT TYPE: Journal
FILE SEGMENT: K
LANGUAGE: English
SUMMARY LANGUAGE: English
AB **Plasmodium** berghei infection in Mastomys natalensis impaired the hepatic mitochondrial, microsomal and cytosolic **glutathione** -S-transferase(s) activity with 1-chloro-2,4-dinitrobenzene as substrate. The enzyme activity was concomitantly decreased with rise in parasitaemia. The decreased enzyme activity due to infection was almost normalized with oral **treatment** of 16 mg (kg body wt) super(-1) of chloroquine for 4 days.

L28 ANSWER 26 OF 30 LIFESCI COPYRIGHT 2005 CSA on STN DUPLICATE 12
ACCESSION NUMBER: 95:120291 LIFESCI
TITLE: **Plasmodium** berghei: Implication of intracellular **glutathione** and its related enzyme in chloroquine resistance in vivo
AUTHOR: Dubois, V.L.; Platel, D.F.N.; Pauly, G.; Tribouley-Duret, J.
CORPORATE SOURCE: Lab. Immunol. et Parasitol., U.F.R. Sci. Pharma. Univ. Bordeaux II, 146 Rue Leo Saignat 33076 Bordeaux Cedex, France
SOURCE: EXP. PARASITOL., (1995) vol. 81, no. 1, pp. 117-124. ISSN: 0014-4894.
DOCUMENT TYPE: Journal

FILE SEGMENT: K
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Glutathione (GSH) plays a critical role in the detoxication and the protection of cells against oxidative stress. In the present study we examined the relationship between the intracellular GSH level as well as glutathione S-transferase (GST), **glutathione** reductase (GR), and **glutathione** peroxidase (GPx) activities and how they relate to **Plasmodium** berghei resistance to chloroquine. Resistant strains (CQR30 and CQR60) were selected in vivo from a sensitive strain (NK65). Marked increases in GSH levels and GST activity within resistant parasites were observed, compared to sensitive parasites. On the other hand, GR and GPx activities were similar in sensitive and resistant parasites. **Treatment** with chloroquine did not influence the intracellular level of GSH, but it was found to significantly decrease GR activity. Intracellular depletion of GSH, by a nontoxic concentration of buthionine sulfoximine (BSO), significantly sensitized the resistant parasites to chloroquine. These results suggest that the P. berghei resistance results from altered GSH and GST levels and activity, respectively, which enable the detoxification of chloroquine in resistant parasites.

L28 ANSWER 27 OF 30 PASCAL COPYRIGHT 2005 INIST-CNRS. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 1993-0401188 PASCAL
TITLE (IN ENGLISH): Inhibition of a **Plasmodium** vinckei **cysteine** proteinase cures murine **malaria**
AUTHOR: ROSENTHAL P. J.; LEE G. K.; SMITH R. E.
CORPORATE SOURCE: Univ. California, San Francisco gen. hosp., dep. medicine, Dublin CA 94568, United States
SOURCE: (The) Journal of clinical investigation, (1993), 91(3), 1052-1056, 15 refs.
ISSN: 0021-9738 CODEN: JCINAO
DOCUMENT TYPE: Journal
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United States
LANGUAGE: English
AVAILABILITY: INIST-5092, 354000036762110380
AN 1993-0401188 PASCAL

L28 ANSWER 28 OF 30 PASCAL COPYRIGHT 2005 INIST-CNRS. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 1991-0437423 PASCAL
TITLE (IN ENGLISH): The effect of malaria infection on paracetamol disposition in the rat
AUTHOR: MANSOR S. M.; EDWARDS G.; ROBERTS P. J.; WARD S. A.
CORPORATE SOURCE: Univ. Liverpool, dep. pharmacology therapeutics, Liverpool Merseyside L69 3BX, United Kingdom
SOURCE: Biochemical pharmacology, (1991), 41(11), 1707-1711, 41 refs.
ISSN: 0006-2952 CODEN: BCPCA6
DOCUMENT TYPE: Journal
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United Kingdom
LANGUAGE: English
AVAILABILITY: INIST-1418, 354000013849410220
AN 1991-0437423 PASCAL
AB The effect of Plasmodium berghei infection, a rodent malarial model, on the disposition of paracetamol (50 mg/kg, i.v.) was investigated in rats. Malaria infection (MI) resulted in a significant decrease in clearance with no change in volume of distribution and a significant prolongation of the elimination half-life of paracetamol in malaria infected rats. Malaria infection also decreased biliary clearance of paracetamol (64%) but not its glucuronide and sulphate conjugates in the bile compared with controls. In addition, **glutathione** conjugates were not detected in bile samples of **malaria** infected rats

L28 ANSWER 29 OF 30 LIFESCI COPYRIGHT 2005 CSA on STN

ACCESSION NUMBER: 91:60183 LIFESCI
TITLE: The antioxidant enzymes glutathione reductase and trypanothione reductase as drug targets. BIOCHEMICAL PROTOZOOLOGY.
AUTHOR: Krauth-Siegel, R.L.; Lohrer, H.; Buecheler, U.S.; Schirmer, R.H.; Coombs, G. [editor]; North, M. [editor]
CORPORATE SOURCE: Inst. Biochem. II, Im Neuenheimer Feld 328, D-6900 Heidelberg, FRG
SOURCE: (1991) pp. 493-505.
ISBN: 0-7484-0001-X.
DOCUMENT TYPE: Book
TREATMENT CODE: General Review
FILE SEGMENT: K
LANGUAGE: English
AB Many parasites including the causative agents of malaria (Plasmodium falciparum) and of Chagas' heart disease (Trypanosoma cruzi) appear to be more sensitive to oxidative stress than their mammalian hosts. In the case of **malaria** we are attempting to develop inhibitors against a host protein, namely erythrocyte **glutathione** reductase, (NADPH + GSSG + H super(+) = NADP super(+) + 2GSH); a flavoprotein whose stereochemistry of catalysis is known in atomic detail. With Chagas' disease, our target protein is trypanothione reductase of T. cruzi). This enzyme, which appears to occur exclusively in trypanosomatids, catalyses the reduction of glutathionylspermidine disulphides by NADPH.

L28 ANSWER 30 OF 30 AGRICOLA Compiled and distributed by the National Agricultural Library of the Department of Agriculture of the United States of America. It contains copyrighted materials. All rights reserved. (2005) on STN
ACCESSION NUMBER: 84:131298 AGRICOLA
DOCUMENT NUMBER: PAR84005577
TITLE: Action of chloroquine on **glutathione** metabolism of **Plasmodium** berghei parasitized red blood cells.
Action de la chloroquine sur le metabolisme du glutathion chez l'hematie parasitee par Plasmodium berghei.
AUTHOR(S): Bhatia, A.; Charet, P.
AVAILABILITY: DNAL (436.8 AN7)
SOURCE: Annales de parasitologie humaine et comparee., 1984 Vol. 59, No. 3. p. 317-320
Publisher: Paris : Masson.
ISSN: 0003-4150
DOCUMENT TYPE: Article
FILE SEGMENT: Non-U.S. Imprint other than FAO
LANGUAGE: French
SUMMARY LANGUAGE: English

=> (malaria or plasmodium)(15A)(nitrosothiol or arginine or glutathione or cysteine)
L29 12 FILE AGRICOLA
L30 115 FILE BIOTECHNO
L31 7 FILE CONFSCI
L32 0 FILE HEALSAFE
L33 0 FILE IMSDRUGCONF
L34 137 FILE LIFESCI
L35 0 FILE MEDICONF
L36 83 FILE PASCAL

TOTAL FOR ALL FILES
L37 354 (MALARIA OR PLASMODIUM)(15A)(NITROSOTHIOL OR ARGININE OR GLUTATHIONE OR CYSTEINE)

=> 137(20A)(treat or administer or treatment or combine or combination)
L38 0 FILE AGRICOLA
L39 4 FILE BIOTECHNO
L40 0 FILE CONFSCI
L41 0 FILE HEALSAFE

L42 0 FILE IMSDRUGCONF
L43 6 FILE LIFESCI
L44 0 FILE MEDICONF
L45 5 FILE PASCAL

TOTAL FOR ALL FILES
L46 15 L37(20A)(TREAT OR ADMINISTER OR TREATMENT OR COMBINE OR COMBINATION)

=> dup rem
ENTER L# LIST OR (END):146
DUPLICATE IS NOT AVAILABLE IN 'IMSDRUGCONF, MEDICONF'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
PROCESSING COMPLETED FOR L46
L47 9 DUP REM L46 (6 DUPLICATES REMOVED)

=> d 147 ibib abs total

L47 ANSWER 1 OF 9 PASCAL COPYRIGHT 2005 INIST-CNRS. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2004-0584813 PASCAL
COPYRIGHT NOTICE: Copyright .COPYRGT. 2004 INIST-CNRS. All rights reserved.
TITLE (IN ENGLISH): Evaluation of cysteine proteases of Plasmodium vivax as antimalarial drug targets: sequence analysis and sensitivity to cysteine protease inhibitors
AUTHOR: NA Byoung-Kuk; KIM Tong-Soo; ROSENTHAL Philip J.; LEE Jong-Koo; KONG Yoon
CORPORATE SOURCE: Department of Molecular Parasitology and Center for Molecular Medicine, Sungkyunkwan University School of Medicine and Samsung Biomedical Research Institute, Suwon 440-746, Korea, Republic of; Department of Tropical and Endemic Parasitic Diseases, National Institute of Health, Seoul 122-701, Korea, Republic of; Department of Medicine, San Francisco General Hospital, University of California, San Francisco, CA, 94143-0811, United States; Bureau of Health Promotion, Ministry of Health and Welfare, Gwacheon 427-721, Korea, Republic of
SOURCE: Parasitology research : (1987), (2004), 94(4), 312-317, 16 refs.
ISSN: 0932-0113 CODEN: PARREZ
DOCUMENT TYPE: Journal
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: Germany, Federal Republic of
LANGUAGE: English
AVAILABILITY: INIST-5859, 354000120484280100
AN 2004-0584813 PASCAL
CP Copyright .COPYRGT. 2004 INIST-CNRS. All rights reserved.
AB **Cysteine** proteases perform critical roles in the life cycles of **malaria** parasites. In **Plasmodium** falciparum, **treatment** of **cysteine** protease inhibitors inhibits hemoglobin hydrolysis and blocks the parasite development in vitro and in vivo, suggesting that plasmodial cysteine proteases may be interesting targets for new chemotherapeutics. To determine whether sequence diversity may limit chemotherapy against Plasmodium vivax, we analyzed sequence variations in the genes encoding three cysteine proteases, vivapain-1, -2 and -3, in 22 wild isolates of P. vivax. The sequences were highly conserved among wild isolates. A small number of substitutions leading to amino acid changes were found, while they did not modify essential residues for the function or structure of the enzymes. The substrate specificities and sensitivities to synthetic cysteine protease inhibitors of vivapain-2 and -3 from wild isolates were also very similar. These results support the suggestion that cysteine proteases of P. vivax are promising antimalarial chemotherapeutic targets.

L47 ANSWER 2 OF 9 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN

DUPLICATE
ACCESSION NUMBER: 2003:37122625 BIOTECHNO
TITLE: Stage-specific profiling of Plasmodium falciparum proteases using an internally quenched multispecificity protease substrate
AUTHOR: Pattanaik P.; Jain B.; Ravindra G.; Gopi H.N.; Pal P.P.; Balaram H.; Balaram P.
CORPORATE SOURCE: P. Balaram, Molecular Biophysics Unit, Indian Institute of Science, Bangalore 560012, India. E-mail: pb@mbu.iisc.ernet.in
SOURCE: Biochemical and Biophysical Research Communications, (03 OCT 2003), 309/4 (974-979), 41 reference(s) CODEN: BBRCA0 ISSN: 0006-291X
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 2003:37122625 BIOTECHNO
AB Novel internally quenched fluorescence peptide substrates containing sequence specific sites for cleavage by multiple proteases were designed and synthesized. The 28 and 29 residue peptides contain an N-terminal fluorescence acceptor group, 4-(4-dimethylaminophenylazo)benzoic acid (DABCYL), and a C-terminal fluorescence donor group, 5-(2-aminoethylamino) naphthalene-1-sulfonic acid (EDANS). Efficient energy transfer between the donor and acceptor groups flanking the peptide sequence was achieved by incorporation of a central .sup.DPro-Gly segment, which serves as a conformation nucleating site, inducing hairpin formation. This multispecificity protease substrate was used to profile the proteolytic activities in the malarial parasite **Plasmodium** falciparum in a stage dependent manner using a **combination** of fluorescence and MALDI mass spectrometry. **Cysteine** protease activity was shown to be dominating at neutral pH, whereas aspartic protease activity contributed predominantly to the proteolytic repertoire at acidic pH. Maximum proteolysis was observed at the trophozoite stage followed by the schizonts and the rings. .COPYRGT. 2003 Elsevier Inc. All rights reserved.

L47 ANSWER 3 OF 9 LIFESCI COPYRIGHT 2005 CSA on STN DUPLICATE 2
ACCESSION NUMBER: 2003:108434 LIFESCI
TITLE: Influence of Chloroquine Treatment and Plasmodium falciparum Malaria Infection on Some Enzymatic and Non-enzymatic Antioxidant Defense Indices in Humans
AUTHOR: Olatunde Farombi, E.; Shyntum, Y.Y.; Emerole, G.O.
CORPORATE SOURCE: Department of Biochemistry, University of Ibadan, Nigeria; E-mail: olatunde_farombi@hotmail.com
SOURCE: Drug and Chemical Toxicology [Drug Chem. Toxicol.], (20030000) vol. 26, no. 1, pp. 59-71. ISSN: 0148-0545.
DOCUMENT TYPE: Journal
FILE SEGMENT: K
LANGUAGE: English
SUMMARY LANGUAGE: English
AB It is known that malaria infection is accompanied by increased production of reactive oxygen species (ROS) and that malaria parasites are sensitive to oxidative damage. This has been proved by the efficacy of some antimalarial drugs that are known to act via generation of ROS when administered clinically or experimentally. There is lack of information on the effect of chloroquine on the antioxidant defense systems of normal and malaria infected humans. Since chloroquine has remained the mainstay of therapeutic regimen in malaria endemic zones, the present investigation was therefore undertaken to study the status of blood antioxidant defense mechanism, and oxidative stress following chloroquine treatment in normal and plasmodium infected humans. Ten healthy persons (5 males and 5 females) with the same age range (18-35 years) were taken as control group. Ten other individuals were treated with 25 mg/kg body with chloroquine over three days. Ten patients with malaria, not under antimalarial therapy were taken as another group, while another set of 10 patients with malaria were treated with 25 mg/kg body weight over three

days. The activity of superoxide dismutase was increased by 23% in individuals treated with chloroquine compared to controls while the activity of the enzyme decreased by 26% in malaria patients and by 43% in **malaria** patients treated with chloroquine. In all the **treatment** groups, the activities of catalase and **glutathione** peroxidase were lowered (P<0.001). Similarly the levels of vitamins A, C, and beta -carotene were decreased in the **treatment** groups while plasma ceruloplasmin was increased in the groups. Glutathione and cholesterol levels were decreased while malondialdehyde level was increased significantly. Chloroquine treatment mediated oxidative stress in the host and this effect was exacerbated in Plasmodium falciparum infected patients administered with the drug.

L47 ANSWER 4 OF 9 LIFESCI COPYRIGHT 2005 CSA on STN DUPLICATE 3
ACCESSION NUMBER: 2002:105824 LIFESCI
TITLE: Cysteine Proteases of Malaria Parasites: Targets for Chemotherapy
AUTHOR: Rosenthal, P.J.; Sijwali, P.S.; Singh, A.; Shenai, B.R.
CORPORATE SOURCE: Box 0811, University of California, San Francisco, CA 94143-0811 USA; E-mail: rosnthl@itsa.ucsf.edu
SOURCE: Current Pharmaceutical Design [Curr. Pharm. Des.], (20020000) vol. 8, no. 18, pp. 1659-1672. ISSN: 1381-6128.
DOCUMENT TYPE: Journal
TREATMENT CODE: General Review
FILE SEGMENT: K
LANGUAGE: English
SUMMARY LANGUAGE: English
AB New drugs to **treat malaria** are urgently needed. **Cysteine** proteases of **malaria** parasites offer potential new chemotherapeutic targets. **Cysteine** protease inhibitors block parasite hemoglobin hydrolysis and development, indicating that cysteine proteases play a key role in hemoglobin degradation, a necessary function of erythrocytic trophozoites. These inhibitors also block the rupture of erythrocytes by mature parasites, suggesting an additional role for cysteine proteases in the hydrolysis of erythrocyte cytoskeletal proteins. Recent studies have shown that the repertoire of cysteine proteases of malaria parasites is larger than was previously realized. Plasmodium falciparum, the most virulent human malaria parasite, expresses three papain-family cysteine proteases, known as falcipains. All three proteases are expressed by trophozoites and hydrolyze hemoglobin at acidic pH, suggesting roles in this process. Falcipain-2 also hydrolyzes ankyrin at neutral pH, suggesting additional activity against erythrocyte cytoskeletal targets. Multiple orthologs of the falcipains have been identified in other plasmodial species. Analysis of orthologs from animal model rodent parasites identified similar features, but some noteworthy biochemical differences between the cysteine proteases. These differences must be taken into account in interpreting in vivo experiments. A number of small molecule cysteine protease inhibitors blocked parasite hemoglobin hydrolysis and development, and inhibitory effects against parasites generally correlated with inhibition of falcipain-2. Some compounds also cured mice infected with otherwise lethal malaria infections. Current research priorities are to better characterize the biological roles and biochemical features of the falcipains. In addition, efforts to identify optimal falcipain inhibitors as antimalarials are underway.

L47 ANSWER 5 OF 9 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN DUPLICATE
ACCESSION NUMBER: 2001:32095899 BIOTECHNO
TITLE: Malaria parasite exit from the host erythrocyte: A two-step process requiring extraerythrocytic proteolysis
AUTHOR: Salmon B.L.; Oksman A.; Goldberg D.E.
CORPORATE SOURCE: D.E. Goldberg, Howard Hughes Medical Institute, Dept. of Molec. Med./Microbiology, Washington University School of Med., St. Louis, MO 63110, United States. E-mail: goldberg@borcim.wustl.edu
SOURCE: Proceedings of the National Academy of Sciences of the

United States of America, (02 JAN 2001), 98/1 (271-276), 18 reference(s)
CODEN: PNASA6 ISSN: 0027-8424
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 2001:32095899 BIOTECHNO
AB Intraerythrocytic malaria parasites replicate by the process of schizogeny, during which time they copy their genetic material and package it into infective merozoites. These merozoites must then exit the host cell to invade new erythrocytes. To better characterize the events of merozoite escape, erythrocytes containing **Plasmodium** falciparum schizonts were cultured in the presence of the **cysteine** protease inhibitor, L-transepoxy-succinyl-leucylamido-(4-guanidino)butane (E64). This **treatment** resulted in the accumulation of extraerythrocytic merozoites locked within a thin, transparent membrane. Immunomicroscopy demonstrated that the single membrane surrounding the merozoites is not erythrocytic but rather is derived from the parasitophorous vacuolar membrane (PVM). Importantly, structures identical in appearance can be detected in untreated cultures at low frequency. Further studies revealed that (i) merozoites from the PVM-enclosed merozoite structures (PEMS) are invasive, viable, and capable of normal development; (ii) PEMS can be purified easily and efficiently; and (iii) when PEMS are added to uninfected red blood cells, released merozoites can establish a synchronous wave of infection. These observations suggest that L-transepoxy-succinyl-leucylamido-(4-guanidino)butane (E64) causes an accumulation of an intermediate normally present during the process of rupture. We propose a model for the process of rupture: merozoites enclosed within the PVM first exit from the host erythrocyte and then rapidly escape from the PVM by a proteolysis-dependent mechanism.

L47 ANSWER 6 OF 9 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 1999:29150307 BIOTECHNO
TITLE: Cysteine protease inhibitors as chemotherapy for parasitic infections
AUTHOR: McKerrow J.H.; Engel J.C.; Caffrey C.R.
CORPORATE SOURCE: J.H. McKerrow, Department of Pathology, VA Medical Center-113B, University of California, 4150 Clement Street, San Francisco, CA 94121, United States. E-mail: jmck@cgl.ucsf.edu
SOURCE: Bioorganic and Medicinal Chemistry, (1999), 7/4 (639-644), 49 reference(s)
CODEN: BMECEP ISSN: 0968-0896
PUBLISHER ITEM IDENT.: S0968089699000085
DOCUMENT TYPE: Journal; Article
COUNTRY: United Kingdom
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1999:29150307 BIOTECHNO
AB Analysis of the evolution, localization and biologic function of papain family cysteine proteases in metazoan and protozoan parasites has provided important and often surprising insights into the biochemistry and cellular function of this diverse enzyme family. Furthermore, the relative lack of redundancy of cysteine proteases in parasites compared to their mammalian hosts makes them attractive targets for the development of new antiparasitic chemotherapy. The treatment of experimental models of parasitic diseases with cysteine protease inhibitors has provided an important 'proof of concept' for the use of cysteine protease inhibitors in vivo. Evidence has now accumulated that cysteine protease inhibitors can selectively arrest replication of a microbial pathogen without untoward toxicity to the host. Furthermore, this can be achieved with reasonable dosing schedules and oral administration of the drug. Initial studies have confirmed the efficacy of **cysteine** protease inhibitors in **treatment** of Trypanosoma cruzi, **Plasmodium** falciparum and Leishmania major. Work on Trypanosoma brucei, the agent of African trypanosomiasis, is

preliminary but also promising. Target validation studies have shown that biotinylated or radiolabeled irreversible inhibitors specifically bind to the cysteine protease targets thought to represent the major activity within the parasite. In the case of T. cruzi, the effect of inhibitors appears to be predominantly in blocking protease processing. Transfection studies using variant constructs have supported this model. Finally, the generation of null mutants for the multiple protease genes in Leishmania mexicana has provided the first genetic support for the key role of this enzyme family in parasite virulence. Safety studies in rodents and analysis of uptake of inhibitors by parasites and host cells suggest that the selectivity of inhibitors for the parasite targets may reside in the lack of redundancy of parasite proteases, the higher concentration of host proteases in intracellular compartments, and differential uptake of inhibitors by parasites. Attempts to elicit resistance to cysteine protease inhibitors in parasite cultures suggest that mechanisms of induced resistance are independent of resistance to the traditional antiparasitic agents. This suggests that cysteine protease inhibitors may provide an alternative to traditional therapy in drug-resistant organisms.

L47 ANSWER 7 OF 9 LIFESCI COPYRIGHT 2005 CSA on STN DUPLICATE 5
ACCESSION NUMBER: 1998:115043 LIFESCI
TITLE: Antimalarial synergy of cysteine and aspartic protease inhibitors
AUTHOR: Semenov, A.; Olson, J.E.; Rosenthal, Ph.J.*
CORPORATE SOURCE: Dept. of Medicine, Box 0811, University of California, San Francisco, CA 94143-0811, USA
SOURCE: Antimicrob. Agents Chemother., (19980900) vol. 42, no. 9, pp. 2254-2258.
ISSN: 0066-4804.
DOCUMENT TYPE: Journal
FILE SEGMENT: K
LANGUAGE: English
SUMMARY LANGUAGE: English
AB It has been proposed that the Plasmodium falciparum cysteine protease falcipain and aspartic proteases plasmepsin I and plasmepsin II act cooperatively to hydrolyze hemoglobin as a source of amino acids for erythrocytic parasites. Inhibitors of each of these proteases have potent antimalarial effects. We have now evaluated the antimalarial effects of combinations of cysteine and aspartic protease inhibitors. When incubated with cultured P. falciparum parasites, cysteine and aspartic protease inhibitors exhibited synergistic effects in blocking parasite metabolism and development. The inhibitors also demonstrated apparent synergistic inhibition of plasmodial hemoglobin degradation both in culture and in a murine **malaria** model. When evaluated for the **treatment** of murine **malaria**, a **combination** of **cysteine** and aspartic protease inhibitors was much more effective than higher concentrations of either compound used alone. These results support a model whereby plasmodial cysteine and aspartic proteases participate in the degradation of hemoglobin, and they suggest that combination antimalarial therapy with inhibitors of the two classes of proteases is worthy of further study.

L47 ANSWER 8 OF 9 LIFESCI COPYRIGHT 2005 CSA on STN DUPLICATE 6
ACCESSION NUMBER: 95:101871 LIFESCI
TITLE: Status of hepatic **glutathione**-S-transferase(s) during **Plasmodium** berghei infection and chloroquine **treatment** in Mastomys natalensis
AUTHOR: Srivastava, P.; Arif, A.J.; Pandey, V.C.
CORPORATE SOURCE: Cent. Drug Res. Inst., Lucknow 226 001, India
SOURCE: INT. J. PARASITOL., (1995) vol. 25, no. 2, pp. 203-205.
ISSN: 0020-7519.
DOCUMENT TYPE: Journal
FILE SEGMENT: K
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Plasmodium berghei infection in Mastomys natalensis impaired the hepatic mitochondrial, microsomal and cytosolic glutathione-S-transferase(s)

activity with 1-chloro-2,4-dinitrobenzene as substrate. The enzyme activity was concomitantly decreased with rise in parasitaemia. The decreased enzyme activity due to infection was almost normalized with oral treatment of 16 mg (kg body wt) super(-1) of chloroquine for 4 days.

L47 ANSWER 9 OF 9 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN

ACCESSION NUMBER: 1993:23054466 BIOTECHNO

TITLE: Malaria antigen and cytokine-induced production of reactive nitrogen intermediates by murine macrophages: No relevance to the development of experimental cerebral malaria

AUTHOR: Kremsner P.G.; Nussler A.; Neifer S.; Chaves M.F.; Bienzle U.; Senaldi G.; Grau G.E.

CORPORATE SOURCE: Landesinstitut fur Tropenmedizin, Engeldamm 62,1020 Berlin, Germany.

SOURCE: Immunology, (1993), 78/2 (286-290)
CODEN: IMMUAM ISSN: 0019-2805

DOCUMENT TYPE: Journal; Article

COUNTRY: United Kingdom

LANGUAGE: English

SUMMARY LANGUAGE: English

AN 1993:23054466 BIOTECHNO

AB The in vitro production of reactive nitrogen intermediates (RNI) by murine macrophages was evaluated in response to heat-stable malaria antigen and cytokines. Malaria antigen, interferon-γ (IFN-γ) and tumour necrosis factor (TNF) induced RNI production in macrophages in a dose-dependent way. RNI production steadily increased over a 2-day period and was enhanced when the malaria antigen was co-incubated with IFN-γ and/or TNF. RNI production induced by either IFN-γ or malaria antigen or a combination of the two was suppressed by pentoxifylline in a dose-dependent manner. Pentoxifylline did not significantly influence TNF-induced RNI production. L-N-monomethyl **arginine** reduced **malaria** antigen, IFN-γ and TNF-induced RNI production when these reagents were used in **combination** or alone. An anti-TNF monoclonal antibody (mAb) reduced IFN-γ-induced RNI production, but did not significantly alter the malaria antigen-induced RNI synthesis by macrophages. The influence of inhibitors of nitric oxide synthase, L-N-monomethyl arginine and N ω-nitro-L-arginine, was studied in experimental cerebral malaria. They did not exert any significant effect on the development of cerebral malaria in Plasmodium berghei ANKA-infected CBA/J mice.

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=> (malaria or plasmodium) and (nitrosothiol or arginine or glutathione or cysteine)
L1          35 FILE AGRICOLA
L2         356 FILE BIOTECHNO
L3           7 FILE CONFSCI
L4           0 FILE HEALSAFE
L5           0 FILE IMSDRUGCONF
L6         365 FILE LIFESCI
L7           0 FILE MEDICONF
L8         227 FILE PASCAL

TOTAL FOR ALL FILES
L9         990 (MALARIA OR PLASMODIUM) AND (NITROSOTHIOL OR ARGININE OR GLUTATH
               IONE OR CYSTEINE)

=> (malaria or plasmodium)(15A)(nitrosothiol or arginine or glutathione or cysteine)
L10         12 FILE AGRICOLA
L11        115 FILE BIOTECHNO
L12          7 FILE CONFSCI
L13          0 FILE HEALSAFE
L14          0 FILE IMSDRUGCONF
L15        137 FILE LIFESCI
L16          0 FILE MEDICONF
L17         83 FILE PASCAL

TOTAL FOR ALL FILES
L18        354 (MALARIA OR PLASMODIUM)(15A)(NITROSOTHIOL OR ARGININE OR GLUTATH
               IONE OR CYSTEINE)

=> l18 and (administer or treatment or treat or administration)
L19          1 FILE AGRICOLA
L20         11 FILE BIOTECHNO
L21          0 FILE CONFSCI
L22          0 FILE HEALSAFE
L23          0 FILE IMSDRUGCONF
L24         15 FILE LIFESCI
L25          0 FILE MEDICONF
L26         15 FILE PASCAL

TOTAL FOR ALL FILES
L27         42 L18 AND (ADMINISTER OR TREATMENT OR TREAT OR ADMINISTRATION)

=> dup rem
ENTER L# LIST OR (END):l27
DUPLICATE IS NOT AVAILABLE IN 'IMSDRUGCONF, MEDICONF'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
PROCESSING COMPLETED FOR L27
L28          30 DUP REM L27 (12 DUPLICATES REMOVED)

=> d l28 ibib abs total

L28   ANSWER 1 OF 30  PASCAL  COPYRIGHT 2005 INIST-CNRS. ALL RIGHTS RESERVED.
      on STN
ACCESSION NUMBER:         2004-0596335   PASCAL
COPYRIGHT NOTICE:         Copyright .COPYRGT. 2004 INIST-CNRS. All rights
                          reserved.
TITLE (IN ENGLISH):       Synthesis and structure-activity relationships of
                          parasiticidal thiosemicarbazone cysteine
                          protease inhibitors against Plasmodium
                          falciparum, Trypanosoma brucei, and Trypanosoma cruzi
AUTHOR:                   GREENBAUM Doron C.; MACKEY Zachary; HANSELL Elizabeth;
                          DOYLE Patricia; GUT Jiri; CAFFREY Conor R.; LEHRMAN
                          Julia; ROSENTHAL Philip J.; MCKERROW James H.; CHIBALE
                          Kelly
CORPORATE SOURCE:         Sandler Center for Basic Research in Parasitic
                          Diseases, Department of Pathology, University of
                          California, San Francisco, California 94143, United
                          States; Department of Medicine, San Francisco General
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Hospital, San Francisco, California 94143, United States; Department of Chemistry, University of Cape Town, Rondebosch 7701, South Africa
SOURCE: Journal of medicinal chemistry : (Print), (2004), 47(12), 3212-3219, 18 refs.
ISSN: 0022-2623 CODEN: JMCMAR
DOCUMENT TYPE: Journal
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United States
LANGUAGE: English
AVAILABILITY: INIST-9165, 354000111973820260
AN 2004-0596335 PASCAL

AB We have synthesized a library of thiosemicarbazones and screened them against three parasitic cysteine proteases, cruzain, falcipain-2, and rhodesain, and against the respective parasite sources of these three proteases, Trypanosoma cruzi, Plasmodium falciparum, and Trypanosoma brucei. The screens identified compounds that were effective against the enzymes and the parasites but also some compounds that were parasiticidal despite a lack of activity against the proteases. Several compounds were effective in killing all tested parasites. These promising lead compounds were tested for general toxicity in mice, and only one produced observable toxicity after 62 h. Our results suggest that thiosemicarbazones represent validated drug leads that kill several species of protozoan parasites through the inhibition of cysteine proteases as well as other novel targets.

L28 ANSWER 2 OF 30 PASCAL COPYRIGHT 2005 INIST-CNRS. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2004-0588673 PASCAL

TITLE (IN ENGLISH): Plasmodium berghei: dehydroepiandrosterone sulfate reverses chloroquino-resistance in experimental **malaria** infection; correlation with glucose 6-phosphate dehydrogenase and **glutathione** synthesis pathway
AUTHOR: SAFEUKUI Innocent; MANGOU Francois; MALVY Denis; VINCENDEAU Philippe; MOSSALAYI Diavad; HAUMONT Gilbert; VATAN Remi; OLLIARO Piero; MILLET Pascal
CORPORATE SOURCE: Unite 3677, Bases therapeutiques des inflammations et infections, Universite Victor Segalen Bordeaux II. 146 rue Leo Saignat, 33076 Bordeaux, France; Laboratoire de Parasitologie, Centre Hospitalier, Universitaire de Saint Andre, Bordeaux, France; UNDP/World Bank/WHO Special Programme on Research & Training in Tropical Diseases (TDR), World Health Organization, Geneva, Switzerland
SOURCE: Biochemical pharmacology, (2004), 68(10), 1903-1910, 53 refs.
ISSN: 0006-2952 CODEN: BCPCA6
DOCUMENT TYPE: Journal
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United States
LANGUAGE: English
AVAILABILITY: INIST-1418, 354000122480280010
AN 2004-0588673 PASCAL

AB In **Plasmodium** falciparum-infected cells or in P. berghei infected mice, increase of reduced **glutathione** (GSH) levels confers resistance to chloroquine (CQ). GSH is synthesized within the cells through a complex biochemical pathway composed of several well known enzymes, in which glucose-6-phosphate dehydrogenase (G6PD) plays an important role. The physiological hormone dehydroepiandrosterone sulfate (DHEAS) is a potent inhibitor of G6PD activity, and G6PD deficiency is known to exert antimalaria protection. This study aimed to investigate the ability of DHEAS to enhance the antimalarial activity of CQ, via an inhibition of G6PD activity and GSH synthesis. Two P berghei CQ resistant